BEHAVIOUR OF SINGLE MOTOR UNITS IN HUMAN SKELETAL MUSCLE

by

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Thesis presented for the Degree of Doctor of Philosophy
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January, 1962

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CHAPTER 1

THE CONTROL OF MUSCLE CONTRACTION BY THE CENTRAL NERVOUS SYSTEM

A. SHERRINGTONIAN CONCEPTS

The pyramidal tracts are the means by which the nervous impulses which excite voluntary movements pass from the motor area of the cerebral cortex to the lower motor neurones. The cell bodies of the lower motor neurones (or "the final common pathway" of Sherrington) are situated in the motor nuclei of the brain stem and the anterior horn cells of the spinal cord. Their dendrites receive impulses directly from the axones of the pyramidal tracts (Sherrington, 1906). Their axones pass into the cranial and spinal nerves and terminate finally in relation with a definite number of muscle fibres. The excitability of "the final common pathway" can be modified by convergence on it of facilitatory and inhibitory extrapyramidal fibres.

This concept held the field until quite recently. It has now been shown (Hoff and Hoff, 1934; Lloyd, 1941) that most of the pyramidal fibres terminate on interneurones which in turn activate the motoneurones of the anterior horn. In addition a whole system of peripheral regulation of motoneurone excitability has been disclosed and this work calls for some summary as it has not as yet been incorporated into clinical thinking.

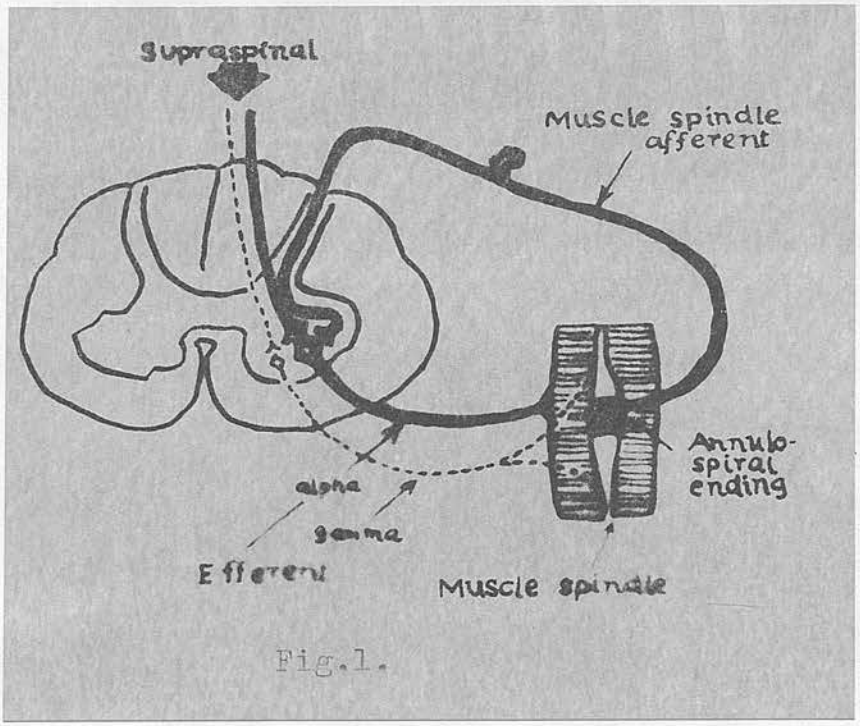

Supraspinal
Muscle spindle afferent
Annulo-spiral ending
alpha
gamma
Efferent
Muscle spindle

Fig.1.

B. THE GAMMA EFFERENT MOTOR SYSTEM

There are two types of motoneurones in the anterior horn of the spinal grey matter. The large motoneurones whose myelinated axones (12-20 μ diameter) have a conduction velocity of 70-120 m. per second are called the alpha motoneurones. The second type is a group of small motoneurones with thin (2-8 μ diameter) myelinated axones. O'Leary et al. (1935) found that stimulation of these small diameter ventral root fibres in mammalia produced no shortening of muscle beyond that caused by the stimulation of large motor fibres. These small fibres are said to constitute about 30 to 35% of the entire efferent outflow from the ventral root (Eccles and Sherrington, 1930). Leksell (1945) called them 'gamma' fibres. He experimented on the cat and found (by selective removal of the alpha fibres) that the gamma fibres supply the intrafusal muscle fibres of the spindles exclusively. The conduction velocity of these fibres was found by him to be 20 to 40 m. per second. His work was later supported by Hunt (1951) and Kuffler et al. (1951).

A simple but incomplete picture of the gamma loop is shown in fig. 1. The gamma fibres take origin from the small anterior horn cells and supply each pole of one intrafusal fibre. They may be distributed to other fibres of the same or different spindles. Fibres of a single spindle may be innervated by more than one spinal segment (Bowden, 1960).

There are two types of sensory endings in a spindle. The thick-fibred annulo-spiral endings (or primary endings) which

surround the non-contractile sector or 'nuclear bag' of the intra-fusal fibres is a stretch receptor, the effective stimulus being the length difference between the intra-fusal and the parallel extrafusal fibres. The second type is the thin-fibred flower-spray ending (the secondary ending). There may be one, two or none of this second type in one spindle. The secondary endings are receptors for reflexes which differ according to the function of the muscle. In general they facilitate flexor reflexes and inhibit stretch reflexes of extensor muscles (Granit, 1955b). When annulo-spiral and flower-spray endings are found together in one spindle, the latter lie to the side of the nuclear bag (Bowden, 1960). The maximum number of flower-spray endings observed in a single de-efferented spindle was five (Boyd, 1959).

The annulo-spiral endings respond to sudden increase of muscle length and excite the motoneurones of the stretched muscle by a monosynaptic reflex (of Hoffmann). The strength of this reflex depends not only on the degree of muscle-stretch but also on the initial length or tension of the intrafusal fibres (i.e. on their pre-extension). A stream of impulses at a frequency of 10-60 per second is transmitted constantly by the gamma fibres to the intrafusal fibres. By this means, 'pre-extension' can be attained in an active manner by actual contraction of the intrafusal fibres. Such a contraction of the intrafusal fibres of the calf muscles can be induced in the human by a strong voluntary contraction of

the upper limb muscles (Jendrassik's manoeuvre). Active 'pre-extension' of the spindles allows the endings to discharge during a maximal voluntary contraction of the entire muscle, even though the stretch receptor is in parallel with the extrafusal fibres.

The other type of receptors, the flower-spray endings, respond to slow changes of muscle length and to enduring stretches, and their activity is suspended entirely during active muscle contraction. They operate on the motoneurones through polysynaptic arc, i.e. by way of one or more internuncial neurones. They seem to be more sensitive and less liable to active regulation, and believed to be the receptors and initiators of the myotatic reflexes of Liddell and Sherrington, or Dehnungsreflexe of Foerster; but their function is still controversial and the mechanism of the 'static' stretch reflex is not so well understood as is the 'phasic' reflex using a monosynaptic arc.

Supra-spinal control

The reticular formation of the brain stem has direct and extensive connections with the gamma motor neurones (Granit and Holmgren, 1955), and through these connections conditioned changes of the reticular formation could be imposed on the gamma fibres at the spinal level. Granit and Kaada (1952) observed in decerebrate cats that stimulation of the anterior lobe of the cerebellum and a certain region of the bulbar reticular formation which previously had been found to

facilitate and inhibit muscle tone and movement (Magoun and Rhines, 1946; Rhines and Magoun, 1946) also facilitated and inhibited the muscle spindle activity. Chlorpromazine greatly reduces activity in the reticular formation and has an inhibitory effect on the gamma firing (Henatsch and Ingvar, 1956). Conversely, adrenaline increases reticular activity, increases the gamma discharge, and causes an increase in the muscle tone in the decerebrate preparation.

Though stimulation of the cortex may influence the muscle spindle activity directly (Granit, 1955a), alteration of the gamma discharge can occur independently of cortical activity (Buchwald and Eldred, in press). Yoshii et al (1957) report that conditioned responses can be detected earlier in the reticular formation than in the cortex, and hence the former seems to have a greater controlling effect on the firing characteristics of the gamma fibres.

C. REFLEX BASIS OF MUSCLE TONE

Sherrington (1906) showed that muscle tone was reflex in nature, being fundamentally based on monosynaptic and polysynaptic stretch reflex. Granit and his co-workers have supported the hypothesis that the excitability of the stretch reflex arc maintaining tone is largely determined by gamma efferent activity. The annulo-spiral endings with the monosynaptic reflex arc forms an adjustable 'servo-mechanism' of muscle length. It is adjustable because its activity

depends on the contraction of the intra-fusal fibres which are innervated by the gamma-efferents. If a particular muscle length is set in advance by the gamma fibres, this servo-mechanism causes muscle contraction by way of mono-synaptic reflex until the extra-fusal muscles accept the adjusted length of the spindles.

There exists in the muscle another servo-mechanism, i.e. muscle tension. The receptors in this case are the Golgi tendon organs which transmit inhibitory impulses to the efferent motoneurones (negative feed back) when the tension exceeds certain limits.

Granit and Kaada (1955) supported the view that the gamma efferent system is activated tonically from the central regions and in its turn, controls the tonic activity of the muscle spindle afferents and that the essential pathway for excitation of muscle, even during voluntary innervation, lies through the gamma system to the intrafusal fibres, thence back through the large spindle afferents which are facilitory for their own and synergistic alpha motoneurones (Granit, 1950; Hunt, 1952), and finally over the monosynaptic reflex arc to the extrafusal muscle fibres which perform the work of the muscle. This indirect system of muscle control sacrifices speed for the advantages of controlled contraction regulated by a "length-servo" rather than by a "tension-servo" in the first instance. That is to say that, for loads within the normal working range of the muscle the recruitment of units and the

firing frequency of the active units is determined by the efficiency with which the muscle contracts to the required length, rather than to the tension it is required to exert. The necessary antecedent contraction of intrafusal fibres has been confirmed for many types of movements. Eldred, Granit and Merton (1953a) observed that acceleration and slowing of the spindle was clearly leading both contraction and relaxation when muscle contraction was elicited by neck reflexes, and the autogenetic inhibition of the spindle bias preceded muscle relaxation in the lengthening reaction.

The interpretation of these findings is that the gamma system not only improves the performance of the voluntary muscle but also acts as an "ignition mechanism" to initiate movement as well as to maintain tonus. In many if not in all voluntary contractions the gamma efferents are first activated, the afferents from the spindles are then facilitated, and the appropriate alpha motoneurones and direct alpha activation come last or together with gamma activity. With this arrangement the sense organs in the muscle are immediately ready to "measure" during the ensuring contraction (Granit, 1955a).

D. THE ADJUSTMENT OF MUSCLE TENSION

(a) Isometric and isotonic contraction:

Muscle behaves as a two component system in which the contractile part lies in series with the elastic component

composed of tendon and connective tissue. As a result, even when the muscle does not change its total length when excited the contractile part can shorten itself and thereby stretch the elastic component. The development of tension of the whole muscle can only occur when these preliminary changes have taken place. Muscular contraction is said to be 'isometric' when both ends of the contracting muscle are fixed, i.e. contraction without any change in its total length. Muscles do not do any 'external' work in isometric contraction; such contractions are seen in anti-gravity muscles maintaining posture. In 'isotonic' contraction, on the other hand, muscle is allowed to contract with change in its total length. This occurs naturally in moving a limb or lifting a weight, etc.

(b) The concept of the motor unit :

Sherrington (1929) defined a motor unit as "an individual motor nerve fibre with the bunch of muscle fibres it activates". Direct evidence concerning tension development of single units as well as information concerning their rate of discharge was first obtained in 1929 by Denny-Brown while studying the stretch-reflex of the isolated soleus muscle of the decerebrate cat. Using another technique, Adrian and Bronk (1929) succeeded, quite independently of Denny-Brown, in recording the electrical activity of the single motor unit and investigated its functional aspects.

Every muscle is represented in the spinal cord by a number of motor nerve cells which is more or less constant in

one species. The number of muscle fibres innervated by a single neurone varies with the function of the muscle. Thus in the ocular muscles of the sheep, there is one motor nerve fibre for only 6-8 muscles fibres (Tergast, 1873; Bors, 1925). In the abducent muscle of the human eye the proportion is 1:9 (Bjork and Wöhlfahrt, 1936). The m. cutaneous dorsi of frog shows a proportion of 1:17 (Lucas, 1909), the m. tenuissimus, 1:20 (Peter and Hart, 1926), whereas the sartorius muscle of rabbit has a proportion of 1:100-125 (Harreveld, 1947). The proportion in the human biceps brachii is 1:1000 (Buchthal and Madsen, 1950) and in gastrocnemius, 1:1400-1700 (Feinstein et al., 1955).

Sherrington (1929) assumed that activity of a neurone would lead to contraction of all the muscle fibres with which it was connected. He called this functional array the "motor unit". Recent investigations show that the innervation of the muscle fibres is much more complicated. A single stimulation of a nerve fibre does not activate its full complement of muscle fibres, and from this fact the concept of "sub-unit" has arisen (Buchthal and Pinelli, 1952; Pinelli and Buchthal, 1953). Motor units with action potentials of very brief duration (1 or 2 m sec.) may be recorded during voluntary contraction of normal muscle. This suggests that 'sub-units' consisting of very few muscle fibres are recordable. Wöhlfart (1949) has found 'sub-units' consisting of only one muscle fibre.

(c) The subliminal fringe (of Sherrington):

The phenomenon of spatial summation is of great importance in the physiology of the nervous system. It has repeatedly been found by different workers that the tension yielded by combined excitation of two different nerves is sometimes greater than the sum of two reflex responses taken singly. This indicates that each afferent while fully activating a certain number of motoneurones acts also on a further number subliminally producing a subliminal 'central excitatory state' (c.e.s. of Sherrington). Some of these subliminally excited motoneurones may be common to a different afferent nerve, so that by overlapping, the c.e.s. of these neurones becomes raised to the threshold of discharge. This is Sherrington's concept of the subliminal fringe. It is of great importance in reflex co-ordination. It enables one level of the nervous system to reinforce the action of another. Thus, sometimes a feeble stretch of an extensor muscle (by itself producing a weak reflex contraction) combined with rotation of the head (which alone produces little activity in the muscle) may give rise to a considerable reflex contraction of the muscle. Or again, the reflex motor response to a constant afferent stimulus may be increased by supraspinal facilitation which lowers the threshold of otherwise subliminal motoneurones.

(d) Adjustment of tension by the activity of motor units:

It has been shown in isolated nerve-muscle preparation that the tension developed in response to maximal shocks is directly proportional to the frequency of stimulation until a maximum tension is reached (Adrian and Bronk, 1929; Brown and Burns, 1949). Adrian and Bronk (1929), using a highly selective concentric needle electrode, investigated also the electrical behaviour of single muscle fibres or of small muscle fibre bundles supplied by single neurones and hence contracting synchronously. The behaviour of such units corresponds in every respect to that of isolated nerve fibres. This technique was also used to show the impulses occurring during moderate contraction, and led Adrian and Bronk to the discovery that the frequency of electrical discharges in individual muscle fibre is the same as that of nerve fibre and that a gradual increase in the strength of contraction is associated with an increase in the frequency and number of active fibres. In other words, the two means by which a strength of contraction is graded, namely frequency of discharge of each unit and number of active units, probably operate together throughout the range of contraction intensities. "Change of frequency is probably the most delicate grading mechanism and change in number of units most effective" (Lindsley, 1935). A number of workers have reported in full agreement (Smith, 1934; Hoefer and Putnam, 1939; Seyffarth, 1941; Weddell et al., 1944; Kugelberg and Skoglund, 1946; Björk and Kugelberg, 1953). Seyffarth

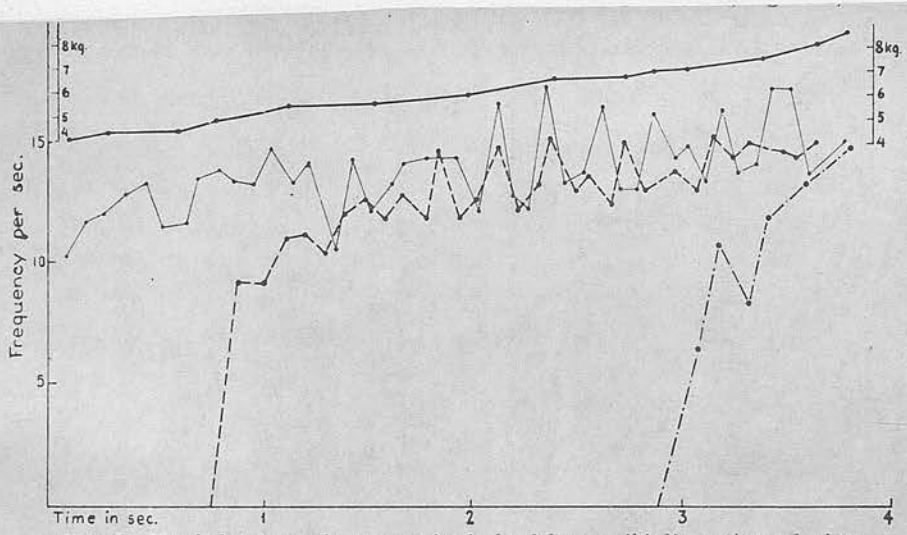


Fig. 5. The behaviour of motor units in healthy m. tibialis anticus, during increase in tension due to isometric ankle flexion at a rise of tension averaging 10 % maximum tension per sec.
The new units (the first oscillation of which marked on the abscissa) rapidly attain the frequency of the first. Ordinates and abscissa as in Fig. 4. The upper curve is the tension recorded during the contraction.

Fig.2.

(1941) showed that, with isometric contraction against increasing loads there was progressive recruitment of motor units. Each started firing at its unique slow rate but rapidly speeded up to assume a rate which then did not increase greatly as the load increased (fig. 2). That is to say, within the "working range" of motor units, the most effective gradation of contraction is by recruitment rather than by change of frequency. There is thus general agreement on this point.

The general application of these findings implies the reasonable assumption that the motor units are randomly distributed in a muscle. Bigland and Lippold (1954) observed that when the ulnar nerve was partly blocked, the maximum voluntary effort did not result in maximum rates of firing of the individual unit which remained accessible to stimulation. A similar relation between frequency and tension to that observed in the unblocked state was demonstrated. They concluded that the tension developed, rather than the degree of voluntary effort made, in some way determines the frequency of motor unit firing.

CHAPTER 2

DIFFERENTIATION OF FUNCTION

A. MUSCLE

Since the work of Ranvier (1889) and later contributions by Hay (1901), Shafer (1912) and Starling (1920), it is a well known fact that striated muscles of many animals have two types of muscle fibres, the red and white. The former contracts more slowly and after a longer latent period than the latter (Grützner, 1887 and Ranvier, 1889), suggesting a 'tonic' and 'phasic' function respectively. Their distribution was studied by several workers, e.g. Grützner (1884), Bidermann (1884), Ranvier (1889), Denny-Brown (1929), Cameron (1929), Gordon and Phillips (1949), Paton and Zaimis (1951), Kruger (1952), etc., but there is no unanimity of opinion, and therefore, "one can attach little importance to the discussion of white pectoral muscles in the fluttering fowl as compared with red in the soaring buzzard" (Biedermann, 1884). Starling's view in this controversy is probably the rational one, that all the striated muscles of higher vertebrates are mixed, although certain small muscles may be almost red or white. Again, their distribution varies even in the same genus as Grützner (1884) found that muscles which are white in the domestic rabbit may be quite red in the wild rabbit.

The problem of division of labour is solved in the cold blooded animals by the existence side by side of anatomically

well defined "tonic" muscle fibres (Gunther, 1949) or the "tonus bundles" (Sommerkamp, 1928), with "phasically" working elements. They also differ electrophysiologically, the "tonic" fibres giving relatively slow, local, non-propagated action potentials of small amplitude, whereas the "phasic" fibres respond with the familiar short and propagated spike of large amplitude (Kuffler, Laporte and Ransmeier, 1947; Kuffler, 1953). The complimentary play of "tonic" and "phasic" innervation can also be demonstrated in the normal, unanaesthetised animal (Hufschmidt, 1956).

B. SPECIALIZED NEURONES

One question which has recently been investigated is whether the alpha motoneurones of the spinal cord can be specialized for tonic or phasic activity respectively. Granit, Henatsch and Steg (1956) came to the conclusion that there are two groups of ventral horn cells in the cat; the "tonic" ones tend to have lower voltage action potentials than the "phasic" ones and are most readily recorded from regions containing the smaller ventral horn cells. These findings are confirmed by Granit, Phillip, Skoglund and Steg (1957). Eccles, Eccles and Lundberg (1957) similarly found that the motoneurones supplying the 'slow' red soleus muscle exhibited a much longer after-hyperpolarization (140-240 msec.) and a slower conduction velocity (50-80 m. per sec.) than the motoneurones which supplied gastrocnemius (after-hyperpolarization = 87 msec., conduction velocity = 90 m. per sec.). The longer

duration of the after-hyperpolarization of the "tonic" motoneurones explains their slower rate of discharge (10-20 per sec.). The "phasic" motoneurones on the other hand are well adapted for initiating quick but transient contractions. It is possible that a similar differentiation of function at the neuronal level may be present even in those species, such as man, where there is no clear distinction between 'red' and 'white' muscle fibres.

C. TOKIZANE'S HYPOTHESIS

A functional differentiation of the motor units in human skeletal muscle has been assumed (literature quoted by Kruger, 1952) though without any direct proof. On the other hand Leksell (1945) and Kuffler, Hunt and Quilliam (1951) postulated that the motor units of warm blooded animals are probably all 'phasic' in nature in the electrophysiological sense, and such animals do not have any units which show local, non-propagated potentials, i.e. "tonic" motor units.

Recently Tokizane (1955) proposed a direct method of examining the problem of functional organisation in human skeletal muscle. He put forward the hypothesis that there are two different functional units in human skeletal muscle which can be recognised by charting the discharge frequency of the single motor units and the variability of rhythm. He described two types of unit, the "Kinetic" or the 'K'-type having a different disposition on a frequency/variability chart from the

"tonic" or the 't'-type (see Chapter 4). This hypothesis of Tokizane was later supported by the independent works of Kawakami (1954), Sala (1958) and Bergamini (1959). Further claims were made that "tonic" units are selectively lost in motor neurone disease (Sala, 1958) and also in progressive muscular dystrophy (Bergamini, 1959), whereas Tokizane himself reports a virtual absence of "kinetic" units in Parkinson's disease (Tokizane, 1955). The implication of these authors is that primary muscular dystrophy and motor neurone disease cause profound flaccid weakness by selectively destroying "tonic" units, while the rigidity without paralysis in Parkinsonism is associated with selective loss of "phasic" units.

The purpose of this thesis is to report work carried out to reinvestigate the control of voluntary contraction of skeletal muscle in the human subject in the light of the "servo" theory and to test Tokizane's hypothesis with regard to differentiation of types of motor units in the normal human and in disease.

CHAPTER 3

PERSONAL OBSERVATIONS ON THE RELATIONSHIP BETWEEN FIRING FREQUENCY OF MOTOR UNITS AND MUSCLE TENSION

INTRODUCTION

When a human muscle contracts during volitional movement, the mean voltage of the electromyogram recorded by surface electrodes increases with the force of contraction (Bayer and Flechtenmacher, 1950; Inman et al., 1952; Lippold, 1952), and in isometric contractions this relationship is always linear (Lippold, 1952; Lenman, 1959). If the velocity of shortening is constant, the relationship remains linear in isotonic contraction, (Bigland and Lippold, 1954). Even when a muscle is fatigued, this relationship remains linear but the slope becomes steeper, so that more electrical activity is associated with a given amount of tension (Sherrer et al., 1954; Edwards and Lippold, 1956). These findings have been confirmed in this laboratory and extended to pathological conditions by Lenman (1959).

Integration of electrical activity recorded by surface electrodes provides a measure of the total number of active muscle fibres per unit of time. The force of voluntary contraction is thus linearly related to the number of muscle fibre contractions per unit of time. The integrated action potential voltages does not, however, distinguish increased units/sec. due to recruitment of extra units from increased

discharge rate of the same number of units.

The relationship between tension and rate of firing reported by Adrian and Bronk (1929) and many others (see Chapter 1, D, d) has been denied by Italian investigators. These workers assert that the motor unit, like all structures of the central nervous system, obeys the "all or none law", not only with regard to the intensity of the excitation, but also to the frequency of its activity; the motor neurone either does not convey impulses to a particular muscle fibre, if a minimal or threshold tension is not reached by the muscle, or if the threshold value is reached, the frequency of the impulses is constant and independent of any factor. The frequency is, according to Gualtierotti and Milla (1942), constant for any one unit at a rate between 6 and 14 per second, with some random fluctuation not related to changes in tension. They investigated the frequency of motor units in the biceps brachii muscle when supporting a load which varied from 1200 to 3000 Gm. They did notice an increase in frequency with increase in tension in a few cases only, but that increase was always found to be within narrow limits and they attributed it to the "normal spontaneous variation in frequency seen in muscle fibres with constant load". Margaria (1946 and 1959) also reported that there was a complete lack of correlation between tension and the frequency of firing of single motor units. The latter was found to be fixed between 10 and 18 per second. The muscle investigated in his series was triceps brachii and the load used varied from 600 to 1200 Gm. He remarked that "the

hypothesis of variability of the impulse frequency from the lower motor neurones cannot stand any more; and the variability of the muscle strength in voluntary or reflex contraction is due solely to a variation of the number of motor units going into activity".

The discrepancy between these Italian reports and those already cited by Adrian and Bronk (1929) and others extends not only to the relationship between tension and the frequency of firing of single motor units but also to the range of frequencies. Adrian and Bronk (1929) noted firing rates from 4-5 up to 50-60 or more per second. Smith (1934) studied the motor unit responses in the biceps and triceps brachii muscles of 8 normal subjects during voluntary contraction. She did not find any frequency of response exceeding 20 per second, but she was unable to record single units during strong contractions. Lindsley (1935) observed that during voluntary contraction, motor unit response usually fell within 5 to 30 per second and seldom exceeded 40 to 60 per second, but he remarked that it is possible for frequency of response to exceed 50 per second during so called "superhuman" feats of strength.

These two points of disagreement are studied in the present series of experiments.

METHODS

1. MUSCLE INVESTIGATED

The first dorsal interosseous muscles were exlusively used in the present series.

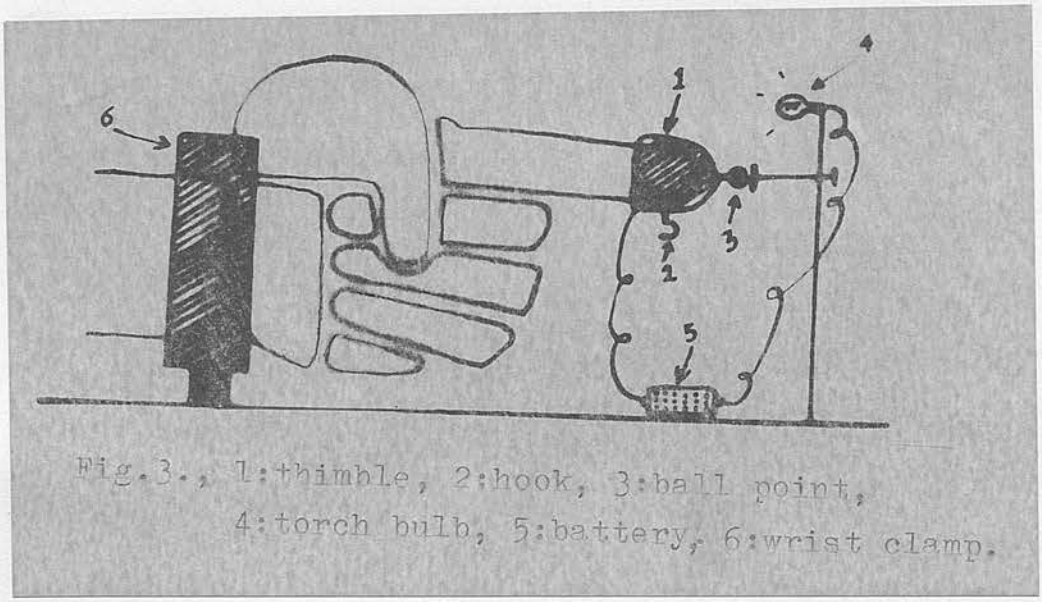


Fig.3., 1:thimble, 2:hook, 3:ball point,
4:torch bulb, 5:battery, 6:wrist clamp.

2. SPECIAL EQUIPMENT AND PRECAUTIONS

To keep the loads used at the standard level, a special frame was devised (fig. 3). The patients' arm was flexed at the elbow and the wrist joint was immobilised by two metal plates (one of which served the function of "earth-plate" for monopolar recording). The subjects were asked to flex all the fingers excepting the index which was kept pointing straight forward. A thimble, which had a hook below it was placed at the tip of the index finger. The thimble also had a "ball point" at its tip. It was so devised that the patients' index finger with the thimble onit, if pointed straight forward, would be in contact with a metal disc pointing backwards from the front part of the frame (the disc was kept at a constant height throughout the present series as far as practicable). Contact between metal disc and the thimble completed a local electrical circuit through a small torch bulb so that any movement of the finger caused the light to go out. The subjects were asked to see that the light was on all through an experiment.

3. TYPE OF LOAD

The isometric tension of the first dorsal interosseous muscle required to keep the index finger straight and at a constant height was assumed to be the same in all subjects (and will be termed Load 1). The muscle was then made to work against different loads, by suspending them from the hook of the thimble (the smallest load was 23 Gm = Load 2, and each

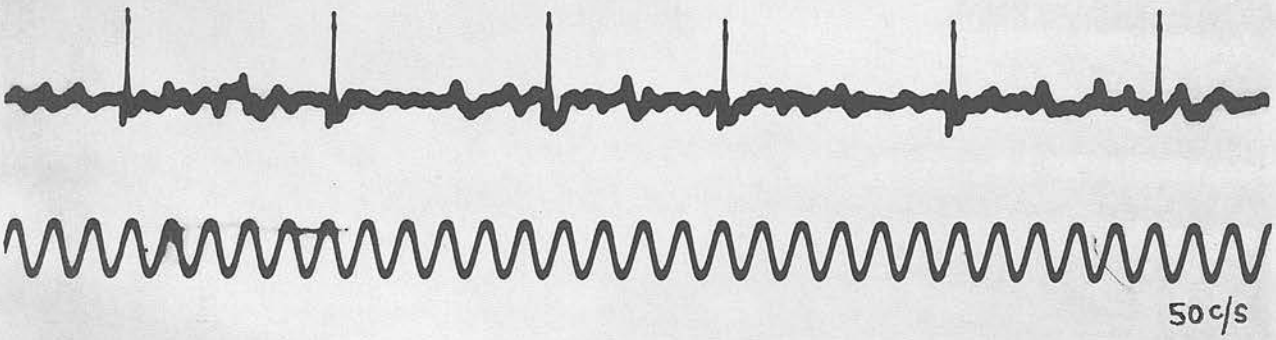


Fig.4.

successive load was double the previous one. The greatest load was 368 Gm = Load 6).

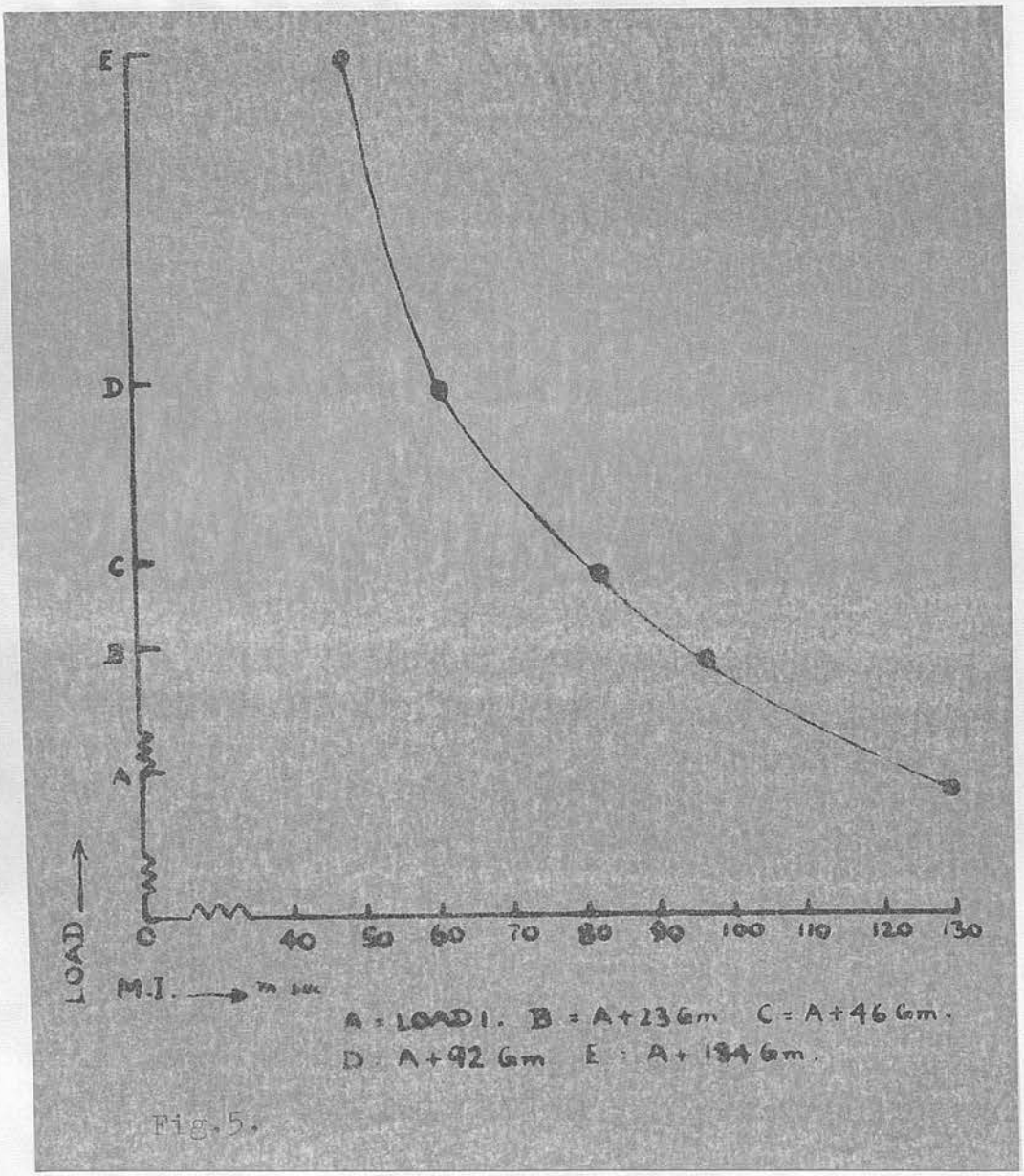
4. RECORDING METHODS

For the present experiments needle electrodes were used, the preparation of which is described in detail in the appendix. These were specially selected to enable single motor units to be identified on the oscilloscope screen even during moderate contraction of muscle. The potential of the needle tip was referred to a remote 'indifferent' electrode on the skin (monopolar recording).

Action potentials of muscles were recorded by inserting the needle electrodes through the skin, amplifying the potentials by a conventional push-pull amplifier, and displaying them on one beam of a two-beam oscilloscope. A time calibration obtained from an Ediswan low-frequency oscillator was displayed on the other beam. Both beams were driven by a 500 msec. time sweep to obtain good resolution and photographed on 70 mm film moving slowly in a direction parallel to the Y axis. An example of the type of record obtained is shown in fig. 4.

5. CRITERIA FOR IDENTIFICATION OF A UNIT

A complete isolation of a single unit was essential for the present study. A record was assumed to arise from a single unit when all the action potentials were approximately of the same shape and when they formed part of regular rhythmic series (Adrian and Bronk, 1929; Denny-Brown, 1929).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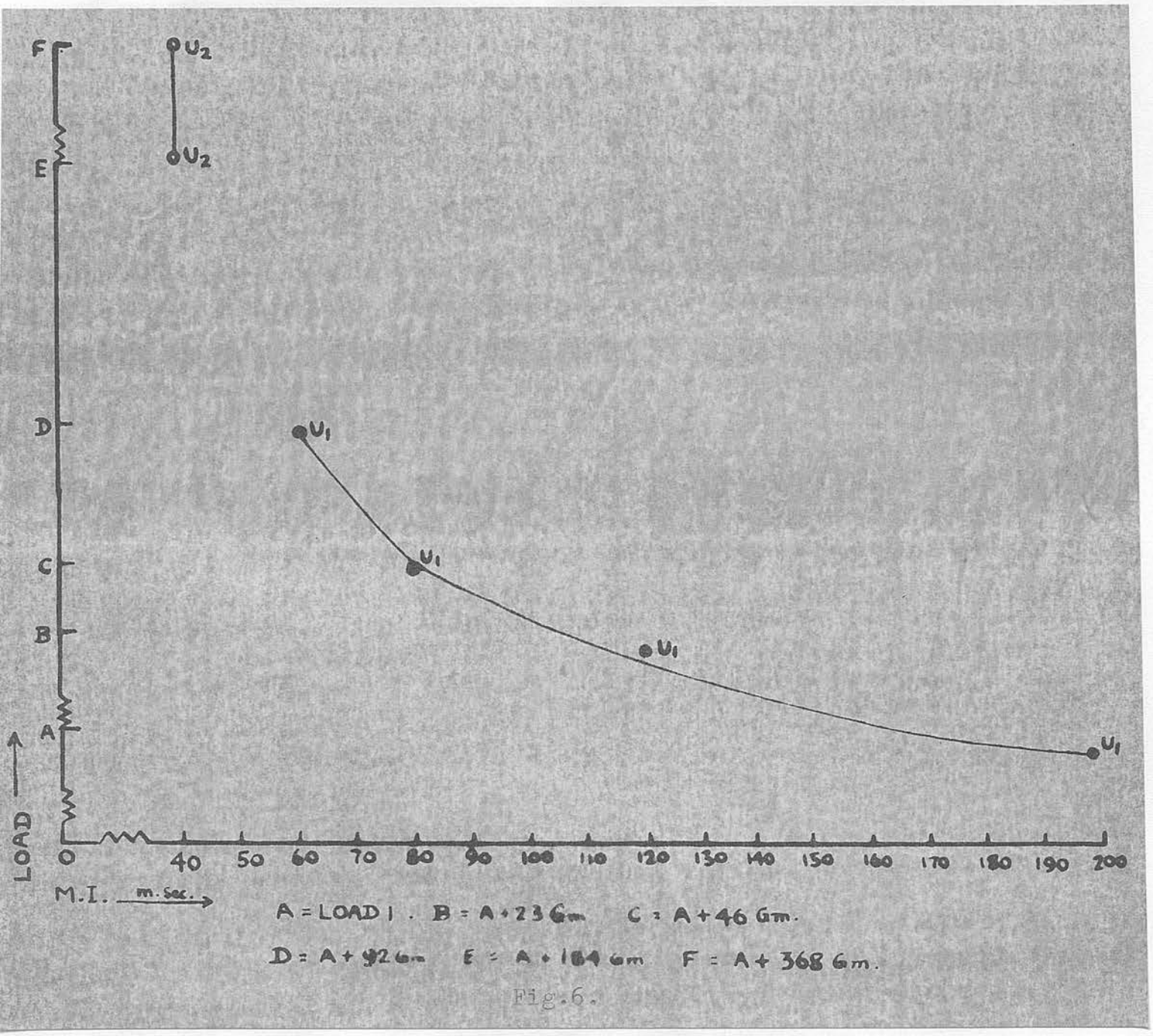
D = A+92 Gm E = A+138 Gm.

Fig.5.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200
M.I. m.sec.
A = LOAD 1 . B = A + 23 Gm C = A + 46 Gm.
D = A + 92 Gm. E = A + 184 Gm F = A + 368 Gm.

Fig.6.

With the electrode used there was no difficulty in distinguishing one unit from another by its distinctive shape for any given electrode position. Though the amplitude might vary slightly from one oscillation to another, generally it was found to be relatively uniform.

EXPERIMENTAL PROCEDURE

A single unit (as defined above) was identified on the oscilloscope screen. It was then recorded while the muscle supported increasing loads (giving a rest between each increment to prevent fatigue of the muscle) till it was no longer recognisable because of the presence of too many units (= normal interference pattern) or till it disappeared to give place to an entirely new unit. When one unit disappeared in the middle of an experiment with increasing load, confirmation was obtained that its disappearance was not due to any shift in the position of the tip of the electrode in relation to that unit by reproducing its rhythmical discharge at a lower tension.

RESULTS

Figs. 5 and 6 are typical examples of the present series which is based on experiments on 14 normal subjects.

Each point in these figures represents the mean interval of 20 to 40 successive spike discharges at that particular tension.

These figures show that there is a definite relationship between tension and the frequency of firing of single motor

units but that it is non-linear. The mean interval of spike discharges diminishes (i.e. frequency of discharge increases) with increasing load and appears to be approaching a limiting value (e.g. Unit U_2 in fig. 6). At higher loads the unit could not be followed in the general interference pattern or it stopped firing and was replaced by a higher threshold unit (fig. 6). Fig. 5 shows that this increase in frequency of the motor unit with increasing load follows a definite pattern. With light loads, a change of 23 Gm. raises the firing rate from 7 to 11 per second. At higher loads, an increment of 92 Gm. was accompanied by a rise in the firing frequency from 17 to 18 per second. This particular unit could not be followed through with increasing loads because of normal interference from too many units, but it is apparent that the relationship between tension and firing frequency is non-linear.

Fig. 6 illustrates another interesting finding. As in the previous experiment, with increase of load from 23 to 46 Gm, the mean interval between spikes (MI) diminished from 200 to 120 msec., i.e. frequency increased from 5 to over 8 per second. When the load was raised from 46 to 92 Gm, the frequency increased from about 13 to 16 per second. On further increasing the load to 184 Gm, the previously active unit (U_1) disappeared altogether and a new unit appeared (U_2) with such a firing frequency as U_1 would have attained if it had continued, and obeyed the same law. When the load was increased to 368 Gm, U_2 maintained the frequency which it reached at the previous load (i.e. 25 per second). This suggests that there might be

some limit to which the frequency of motor units can be raised with increasing tension. It seems also that this limiting frequency varies with different motor units. That of U_1 in fig. 6 seems to be about 16 per second (it disappeared altogether on increasing the load) and that of U_2 seems to be about 25 per second, as it maintained that frequency even on increasing the load considerably. The motor unit of fig. 5 seems to have its frequency limit somewhere about 20 per second (it is impossible to say categorically about it, as this unit could not be recognised on increasing tension after it attained a frequency of 18 per second but from the slope of the tension/MI curve it seems that it would be unlikely for it to reach a frequency much over 20 per second.

DISCUSSION

The interesting feature of the relation between tension and frequency of motor unit discharge during voluntary isometric contraction is the comparatively small range through which the firing rate varies. Bronk (1930) observed that as the rate of stimulation of a muscle is increased, the economy or amount of tension-time maintained per unit of energy expended increases. He suggested that this was mainly due to a greater degree of fusion of muscle twitches, but that there was no further increase in economy with frequencies above that needed to produce a complete tetanus. This is in accordance with Hill's (1949) "active state" theory which states that "the shorter the interval between stimuli, the less the active state declines

between each successive contraction and therefore, the less the energy required to maintain a given amount of tension-time". Thus increase of tension by recruitment of new units rather than by change in frequency of the already active units would lead to greater economy after these low threshold units have reached a certain limit. The maximum frequency obtained by a particular motor unit in the course of muscular contraction is economical of energy since the maximum tension is developed by the unit when its firing rate is such as to ensure fusion of twitches to "tetanus", a principle which applies to the unit as to the muscle as a whole (Bronk, 1930). The critical frequency at which the fusion just begins always depends on the "active state" of the contractile element of the muscle fibre (Hill, 1949). An individual unit starts firing when its threshold tension is developed by the contracting muscle. Its firing rate then increases rapidly up to a limit when it produces complete tetanus, the beginning of which can be seen in the tension/MI curve when the curve bends and gradually becomes a straight line parallel to the tension axis (fig. 6). At this point, when the motor unit has reached its tetanic level, any increase of load is not accompanied by an increase in the rate of firing. It is in keeping with Matthews (1959). This is the probable explanation for the failure of Gualtierotti et al. (1942) and Margaria (1946 and 1959) to find any relationship between tension and the frequency of motor unit discharge, because they started with a very high initial load (600 to 1200 Gm.).

Gualtierotti and Milla (1942) criticised the recording technique, particularly the electrode used by Adrian and Bronk (1929). They thought that Adrian's electrodes were at a macroscopic distance from each other (being co-axial or "concentric" needle electrodes), so a great number of motor units "presumably 30-40" were interposed between them. Hence the spikes registered, though 'apparently' similar, were not due to a single motor unit "but to a few of them whose positions towards the electrodes were very much the same, and so is therefore the amplitude of the potentials". Margaria (1946) supported this criticism by doing "a very minute analysis of Adrian's recordings". Moreover, Adrian and Bronk (1929) experimented on paretic muscles which have higher frequencies than normal muscles (Weddell et al., 1944) (see also Chapters 4 and 9). These may be the reasons why Adrian and Bronk found such a high frequency of motor unit discharge (50-60 or more per sec.) even from large peripheral muscles. Margaria (1946) studied the rhythm of activity of motoneurones and observed that "in voluntary contraction of man, the frequency of electrical activity of single motor unit is 10-18 per second, and is independent from tension of the muscle". His observations are based on the following facts.

Brock et al. (1952) observed that a discharge of an afferent motoneurone is followed by a phase of subnormal excitability. This is due in part to a complicated inhibitory feed-back via the recurrent collaterals of the motor axones to Renshaw cells, and by inhibitory interneurones back to the

corresponding anterior horn cells (Holmgren and Merton, 1953; Eccles et al., 1954). This inhibitory phase following a discharge is also called 'Renshaw inhibition' (Renshaw, 1941 and 1946). All spinal motoneurones possess such a feed back system. In man under normal conditions this inhibition lasts from 60 to 120 msec (Margaria et al., 1958). This is constant within 1-2% for any one motoneurone (Fiorentini, 1958). Margaria (1959) suggested on the basis of these facts that the discharge frequency of a motoneurone must vary inversely with the period of Renshaw inhibition and so a motoneurone with an inhibitory phase of 60 msec. will have a maximum firing frequency of 17 per second, and those with 120 msec. have a maximum frequency of 8 per second. His observations on the triceps brachii muscle during voluntary contraction showed that the frequency of motor units varied from 10 to 18 per second. "Therefore", he suggests, "there exists in motoneurones a maximum firing frequency which is strictly controlled by a reverberating circuit".

But there are serious objections to his present theory. Granit (1958) as well as Eccles (1958) showed that the motoneurones of a muscle have a differential "feed-back" mechanism, so that the frequencies of individual motoneurones may be entirely different with one and the same central excitatory state. Again, according to Wesslau (1952-53), there is only a rather "loose" relation between the discharge frequency and the duration of the inhibitory phase after a proprioceptive reflex, and this is thoroughly understandable on the assumption

of different qualities of motoneurones. Margaria's observation that the frequency limit of motor units in human triceps brachii muscle is 10-18 per second may be true (as some units may reach a tetanic frequency round 18 per second), but his inference that this must be the limit for all motor units is unacceptable.

In view of the different maximal frequency of different motor units (figs. 5 and 6), one cannot escape the assumption that there are motor units of different fusion frequency not only in different muscles but also in one and the same muscle. The work of Bigland and Lippold (1954) supports this assumption. Motor units of ocular muscles fire at rates up to 175 per second (Reid, 1949; Pulfrich, 1952; Björk and Kugelberg, 1953), while muscles serving posture, e.g. leg muscles, have units firing in the range of about 10 per second, but reaching 50 per second only rarely (Adrian and Bronk, 1929; Denny-Brown, 1929). If the maximum frequency represents the fusion limit, this must be considerably higher for ocular than for the leg muscles, and the natural corollary is that the higher the fusion limit of a motor unit the more quick and precise is the movement, and the lower the fusion limit, the more is its function postural and its contraction uniform. It is quite possible that "kinetic" and "tonic" units differentiated in this way by their tetanus fusion rates exist in different proportions in different muscles. This is not simply a matter of variations in the rhythmicity of units as in Tokizane's hypothesis (see Chapter 4), but of definitely different, sharply separate and functionally unequivocal muscle fibres such as were observed by Gordon and

Phillips (1953) in their experiments on the anterior tibial muscles of the cat. Thus, in all probability some motor units are present in one muscle which are specially designed for rapid movement and display of power, and others more adapted for posture, and their differential characteristic is their fusion frequency.

It seems therefore reasonable to infer that the preferred frequency of a motoneurone discharge is tuned to the anatomical characteristics of the individual groups of muscle fibres (Hufschmidt, 1959) and thereby to its mechanical efficiency. Functional differentiation of human motor units seems to lie in this plane. More light will no doubt be shed on this fascinating problem by further research work in future but this is beyond the scope of the present work. The observations reported and discussed in this chapter confirm the views of Adrian, Seyffarth and others that motor units increase their rate of firing with increasing development of tension up to a limiting frequency which is characteristic of each unit. The contrary reports by Italian workers are not confirmed.

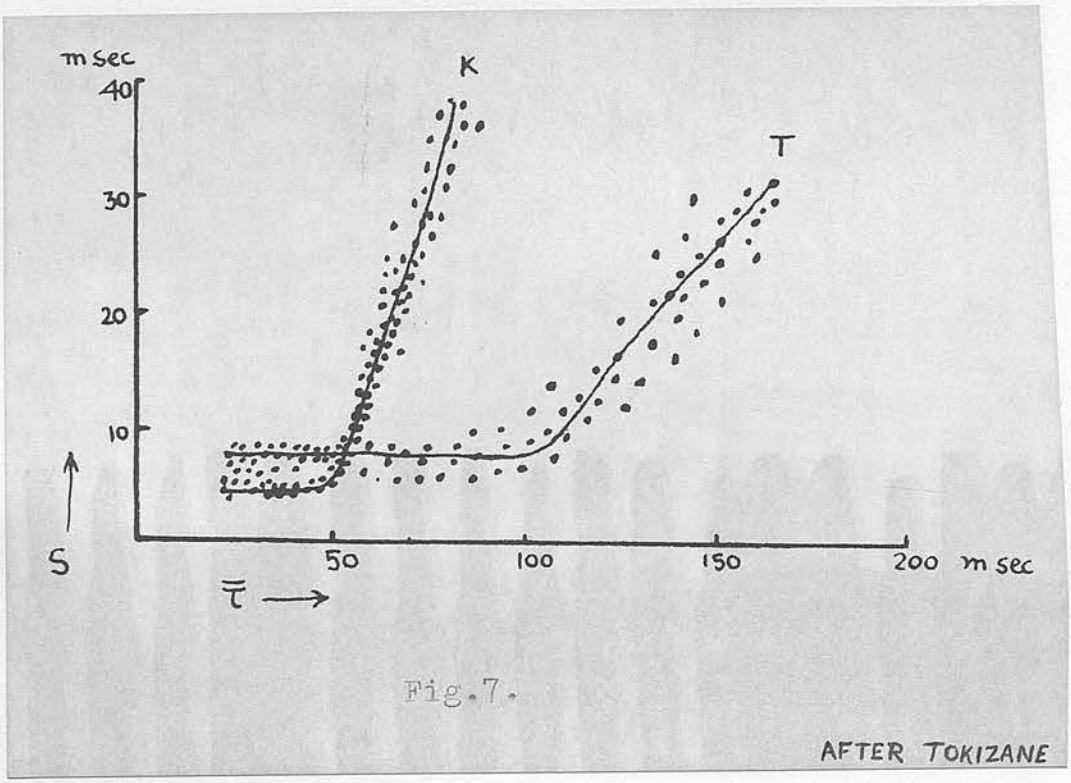


Fig.7.

AFTER TOKIZANE

CHAPTER 4

INVESTIGATION OF TOKIZANE'S HYPOTHESIS

INTRODUCTION

The Japanese worker Tokizane (1955) recently proposed a direct method of examining the problem of functional organisation in human skeletal muscle. It is well known that the frequency of discharge of a single motor unit (Neuromuscular Unit = NMU, as Tokizane calls it) varies during voluntary contraction even when the force of contraction is kept at a constant level. This variability is greater at weak contraction and discharge becomes more rhythmical as the firing rate increases with greater contraction. Tokizane examined the relation between the interval between successive discharges (reciprocal of the firing rate) and the variability from regular rhythm. He chose the standard deviation (S) as an indicator of the range of variation, and the mean spike interval ($\bar{\tau}$) as indicating the contraction intensity. These values "which were obtained by measuring and then calculating from a series of spike recordings" were plotted with S on the ordinate against $\bar{\tau}$ on the abcissa (fig. 7). He tried to obtain "as many $\bar{\tau}$-S points as possible with each muscle", by following the same procedure, "while varying NMU discharge and contraction intensity as much as possible "from various regions. The resultant pictures vary in different muscles and since I worked entirely on muscles in the upper extremity, I shall describe Tokizane's findings in these muscles only.

As can be seen in fig. 7, which is reproduced from Tokizane (1955), these $\bar{\tau}$-S points fall naturally into two groups which are represented by two curves, K and T, differing from each other in position and in course. The curve K is parallel to the abscissa up to $\bar{\tau}$ of 50 msec. and ascends thereafter when $\bar{\tau}$ exceeds 50 msec. Curve T is horizontal up to $\bar{\tau}$ of 100 msec. and then rises more gradually thereafter than the K curve. In other words, the NMUs which are represented by the K curve have minimum variation in spike intervals for firing frequencies exceeding about 20 per second, and their variation becomes gradually greater as the frequency falls below this rate. On the other hand, the NMUs represented by the T curve have a minimum variation with firing frequencies as low as 10 per second, and when the frequency is slower than this, their variation increases more gradually than in the former. This indicates that the latter NMUs are capable of maintaining a smoother contraction as they have low variability even when the contraction is substantially weaker. Assuming that the muscular movements can be divided into so-called "phasic" fast movements and "tonic" sustained movement, Tokizane considered that NMUs following the K curve showed properties of a "phasic" type of discharge, and those following the T curve had a "tonic" type of discharge, reflecting appropriate differences in function. He termed them "kinetic" and "tonic" units respectively, and suggested that they might form a functional differentiation of muscle units having the same end result as the red and white muscle fibres of lower animals.

Fig.8.

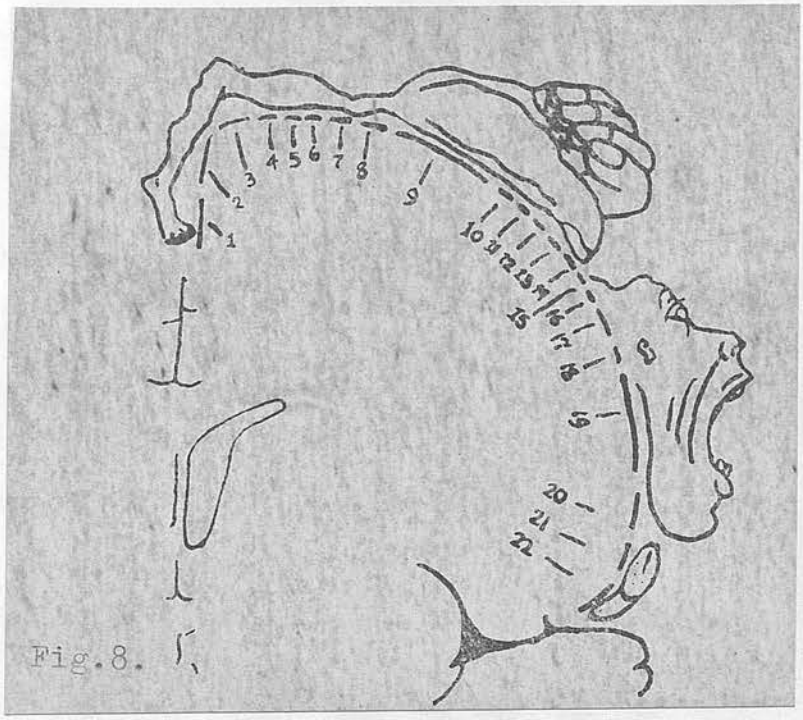


Fig.8.

1.toe.
2.ankle.
3.knee.
4.hip.
5.trunk.
6.shoulder.
7.elbow.
8.wrist.
9.palm.
10.little finger.
11.third finger.
12.middlefinger.
13.index finger.
14.thumb.
15.neck.
16.fore head.
17.eyelid & eyeball.
18.face.
19.lips.
20.lower jaw.
21.tongue.
22.swallowing.

Fig.9.

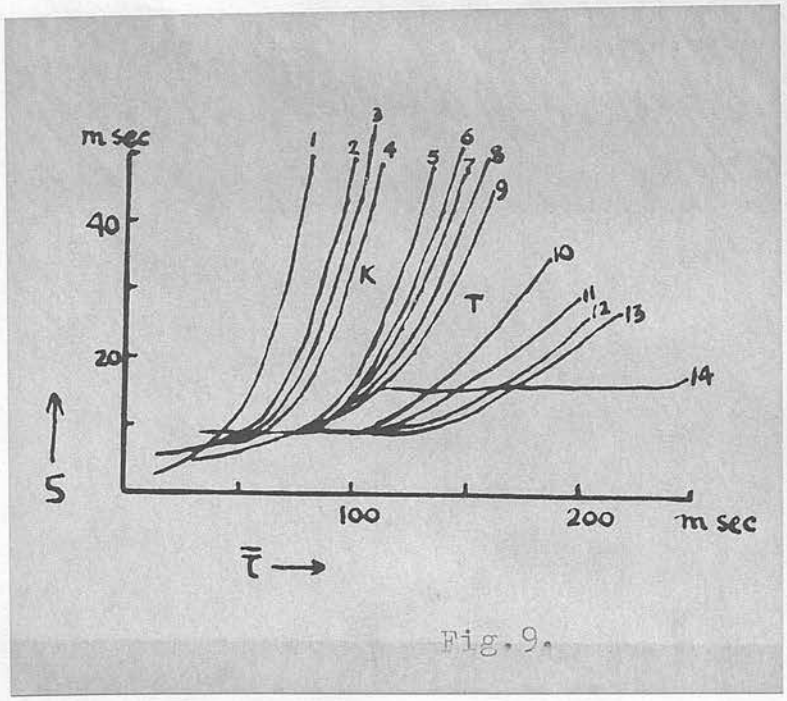


Fig.9.

1.levator palpebrae superioris.
2.lingual muscle.
3.facial muscle.
4.forearm muscle.
5.M.brachialis.
6.same as 1.
7.leg & thigh muscles.
8.lingual muscle.
9.same as 3.
10.same as 4.
11.same as 5.
12.M.sphincter ani externus.
13.same as 7.
14.same as 12.

Different muscles appear to be specialised in the human for different types of functions. Such differentiation, he suggests, "probably results from variance in the percentages of composition between the two kinds of NMUs which are the fundamental functional units". Thus, muscles which are capable of fast motion, e.g. facial muscles, muscles of tongue, small muscles of hand, etc., are considered to consist of an overwhelmingly large number of "kinetic" NMUs, while muscles like soleus, have a greater number of "tonic" NMUs as they are mostly used for maintenance of erect posture or walking requiring a prolonged contraction.

Tokizane then drew some analogy between the famous chart of motor representation in area 4 of human cerebral cortex (Penfield and Rasmussen, 1952) (fig. 8) with his own chart of preponderant unit type in various muscles (fig. 9), and came to the conclusion that $\bar{\tau}$ -S curves for muscles which have wide representation in area 4 of the motor cortex are displaced towards the left, and those having a narrow representation are displaced to the right of $\bar{\tau}$ -S plots. In other words, muscles whose $\bar{\tau}$ -S curves have a short horizontal part (K-type) and have a large area of representation in the motor cortex, are capable of more delicate and swift movement, while muscles having curves with long horizontal part (T-type) and a small area of representation in area 4 are specialized for long sustained contraction. Without experimental proof whatsoever, he deduced that "muscles having curves with longer horizontal parts (tonic) are more dependent on the neural activity of the central motor system (including the spinal cord) 'outside' area

4 of the motor cortex (extra pyramidal) and vice versa". This concept was introduced to explain some discrepancies observed by Tokizane himself. He noted, for instance, that the horizontal part of a curve could be extended to the right by training in the holding of a posture. This lability is not predictable from his basic hypothesis, so he then hints at the possibility that the horizontal part of the curve of each unit represents that part of its firing range under spinal control. By inference, the ascending part is presumed to be cortical.

Granit and Holmgren (1955) suggest that voluntary contraction may be initiated by a gamma efferent discharge which alters the 'bias' of muscle spindles, and the 'misalignment' signal so generated activates the alpha motoneurones (see Chapter 1, B and C). The presence of a horizontal part in a $\bar{\tau}$-S curve (with low variability) is an indication of "controlled" contraction. On the Granit theory this is afferent controlled. Should information from the length and tension receptors be cut off, the regulatory mechanism would fail. In consequence, the horizontal part of the $\bar{\tau}$-S curve would either be shortened or disappear altogether. Tokizane claims to have confirmed that this happens in patients with tabes dorsalis. He found that the point of inflection of their $\bar{\tau}$-S curves was shifted to the left (K-type) and no curves of T-type were found at all. "This indicates", he says, "that in tabes dorsalis patients, the muscular contraction has a weak spinal element while the cortical element plays the principle role".

The existence within a group of extensor muscles in some animals of a slowly contracting deep component and rapidly contracting superficial component was reported by Denny-Brown (1929) and later supported by Gordon and Phillips (1953) who found that the cat's tibialis anterior (functionally a flexor muscle) also has rapidly contracting fibres superficially and slow fibres near its deep surface; but they also noted that "certainly there is no anatomical line of distinction between the rapid and the slow elements, and although the deeper part of the muscle is usually of a darker red in colour, the red and pale fibres are wedded in one muscle".

By calculating the standard deviation and the mean intervals of the frequency of discharge of NMUs, Tokizane claims to have noticed that, "of the two muscles, one superficial and one deep, the superficial one shows $\bar{\tau}$-S curves more displaced towards the left, i.e. 'kinetic' predominance, than the deeper one". He also reports that the superficial and the deep strata of the same muscle have different NMUs serving different functions. The superficial part has more "kinetic" units than the deeper part which has predominantly "tonic" units.

This hypothesis of Tokizane on the functional organisation of normal human striated muscle was later supported by Kawakami (1954), Sala (1958) and Bergamini (1959). Bergamini not only supported Tokizane's findings in normal healthy muscle, but found some interesting deviations from normal in patients suffering from progressive muscular dystrophy. After calculating the standard deviation and the mean firing intervals

of motor units as before, and drawing the $\overline{\tau}$-S curves, he found that almost all the NMUs, in these patients, are disposed along and around the K-curve, and none is found along the T-curve. On the Tokizane hypothesis this would be interpreted as preponderance of damage to T-type units in muscular dystrophy.

Sala (1958) made the same finding (apparent loss of T-type curve) in motor neurone disease, an entirely different condition of neurogenic origin.

Apart from experiments on normal muscle, Tokizane made "a few" observations on patients suffering from Parkinson's disease. He reported a virtual absence of K-type curves in this disease.

The purpose of the experiments presented in this chapter is to examine whether there is, in fact, any such functional organisation of motor units in human skeletal muscle recognisable by the Tokizane method, and whether there is disappearance of any particular type of unit in any disease as is suggested by these workers.

METHODS

1. MUSCLE INVESTIGATED

The first dorsal interosseous muscles were mainly used to examine Tokizane's hypothesis. The purpose of selecting this muscle is two-fold. Firstly, it is one of the small muscles of the hand and so capable of quick contraction. Secondly, it

is responsible for the movement of the index finger which is widely represented in area 4 of the motor cortex. Hence, if Tokizane's hypothesis is correct, the NMUs from this muscle should be disposed predominantly along the 'K'-curve, and should have a short horizontal part.

Biceps brachii muscles were selected to see whether different strata of the same muscle have different functional units.

2. SPECIAL EQUIPMENT AND PRECAUTIONS

As shown in Chapter 3, there is a definite relationship between the tension and the frequency of firing of motor units, the frequency increasing with increasing tension during the early part of a voluntary contraction. Tokizane took no account of the tension developed by contraction of muscle in his experiments. I considered that the behaviour of motor unit activity could only be interpreted in the light of the tension produced by the contraction.

To keep the loads used at standard level, a special frame was therefore devised (fig. 2) for use when experiments were carried out on the first dorsal interosseous muscles (see Chapter 3 for detail).

3. TYPE OF LOAD

A smaller range of loads was used in this series. The weight of the forefinger (i.e. the isometric tension of the first dorsal interosseous muscle required to keep the index

finger straight and at a constant height) was also termed Load 1 (see Chapter 3). The muscle was then made to work against a load by suspending a weight (23 and 46 Gm.) from the hook of the thimbles (i.e. Loads 1, 2 and 3 were used in these experiments).

When biceps brachii was investigated (to see whether different strata of this muscle has different functional NMUs), the degree of flexion at the elbow was kept constant as far as practicable for all the identical experiments in the present series.

4. RECORDING TECHNIQUE AND EXPERIMENTAL PROCEDURE

Same as in Chapter 3.

5. MEASUREMENT AND CHARTING

For the present investigations mean deviation (MD) was used instead of standard deviation (S) as calculation of MD is simpler and it is a suitable measure of variability.

Tokizane is vague not only about the muscle tension he used in his experiments, but about the method of obtaining individual 'points' in his charts. He states that these points "were obtained by measuring and then calculating from a series of spike recordings", but it is nowhere explicitly stated that each curve represents the behaviour of a single NMU.

The illustrations of the present series will therefore chart the relationship between mean firing interval (MI) and

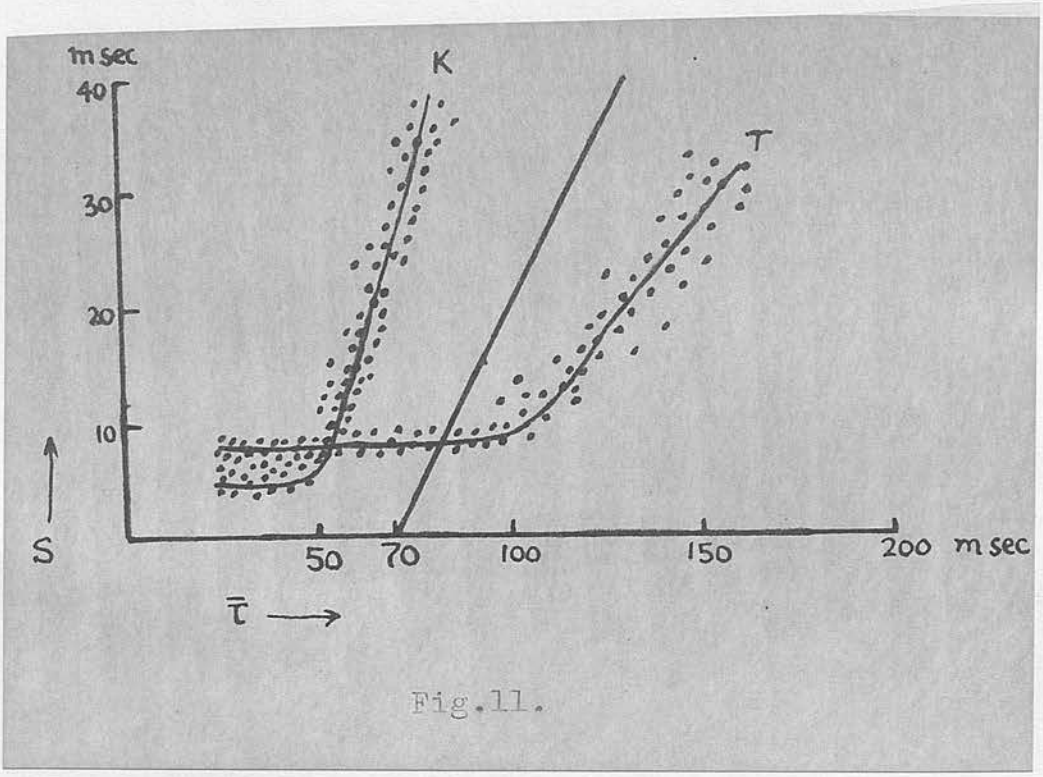


Fig.11.

mean deviation of the intervals (MD), i.e. MĪ/MD instead of $\bar{t}$ -S curves. Unless indicated by separate symbols, each chart will refer to observations on one unit only. Values for MĪ and MD are calculated from measurement of the interval between 4 to 8 discharges of the motor unit spike. MĪ is plotted on the abscissa and MD on ordinate.

6. REFERENCE LINE

A line drawn from MĪ = 70 msec. with zero deviation at 45° from the abscissa clearly separates the two curves of Tokizane (fig. 11). The significance of this line will be discussed later.

MATERIAL

1. NORMALS

Total number = 30. These were colleagues, medical students and patients with idiopathic epilepsy but with no known abnormality of muscular innervation.

2. WEAK MUSCLES

(Paresis due to upper motor neurone lesions were excluded)

Total number = 41.

(a) Myogenic:

(i) Muscular dystrophy - 15 cases.

(ii) Dystrophia myotonica - 3 cases.

(b) Neurogenic:

(i) Motor neurone disease - 15 cases.

(ii) Traumatic injury of ulnar nerve at the elbow - 2 cases.

(iii) Hypertrophic polyneuritis - 2 cases.

(iv) Paresis of brachio radialis muscle of unknown aetiology - 1 case.

(c) Periarthritic (rheumatoid arthritis) - 3 cases.

3. NORMAL POWER WITH ABSENT DEEP REFLEXES

Total number = 6.

(a) Tabes dorsalis - 3 cases.

(b) Friedreich's ataxia - 3 cases.

4. PARKINSONIAN RIGIDITY

Total number = 30.

Of these 27 were due to Paralysis agitans and 3 were probably post-encephalitic in type.

Only one of these patients had true unilateral Parkinsonism. The others had bilateral involvement, the degree of rigidity varied on the two sides.

Results of this investigation are given in the next chapter.

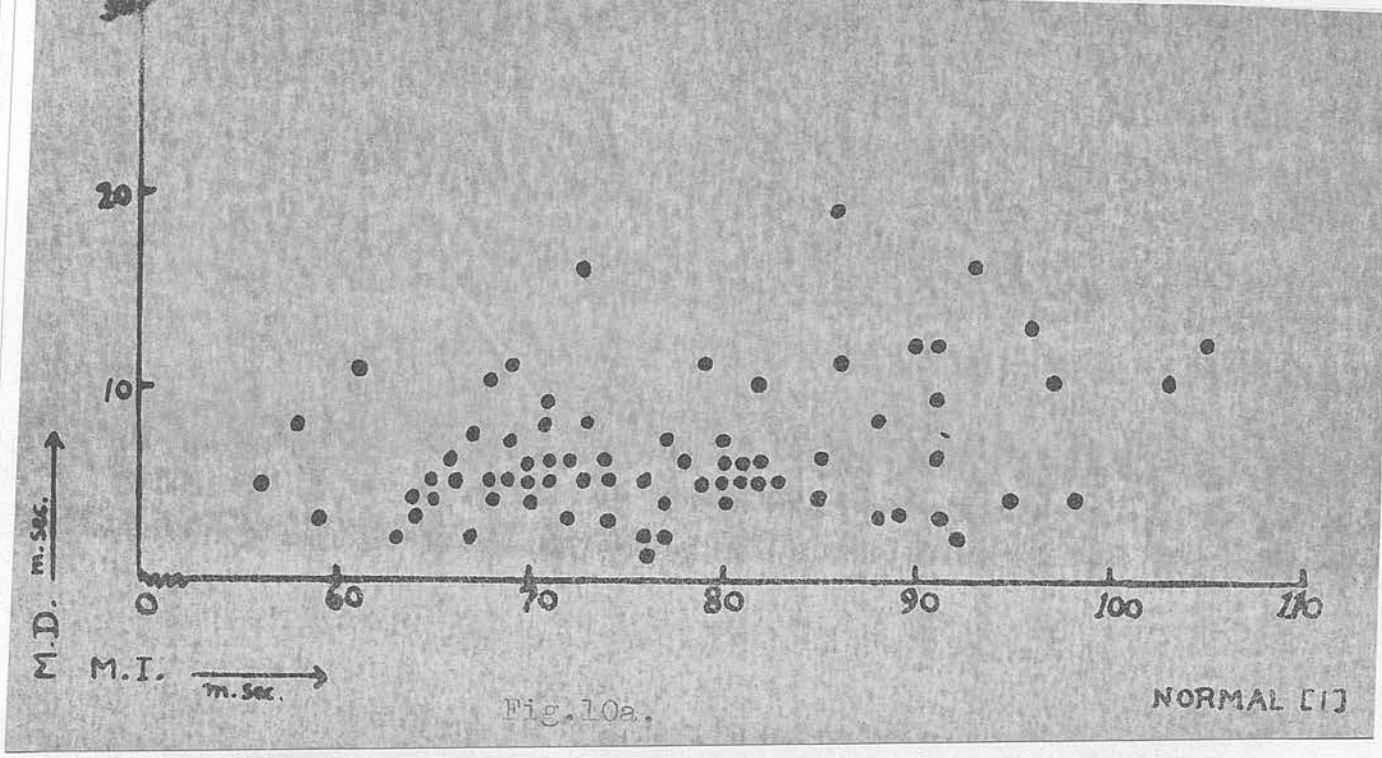


Fig.10a.

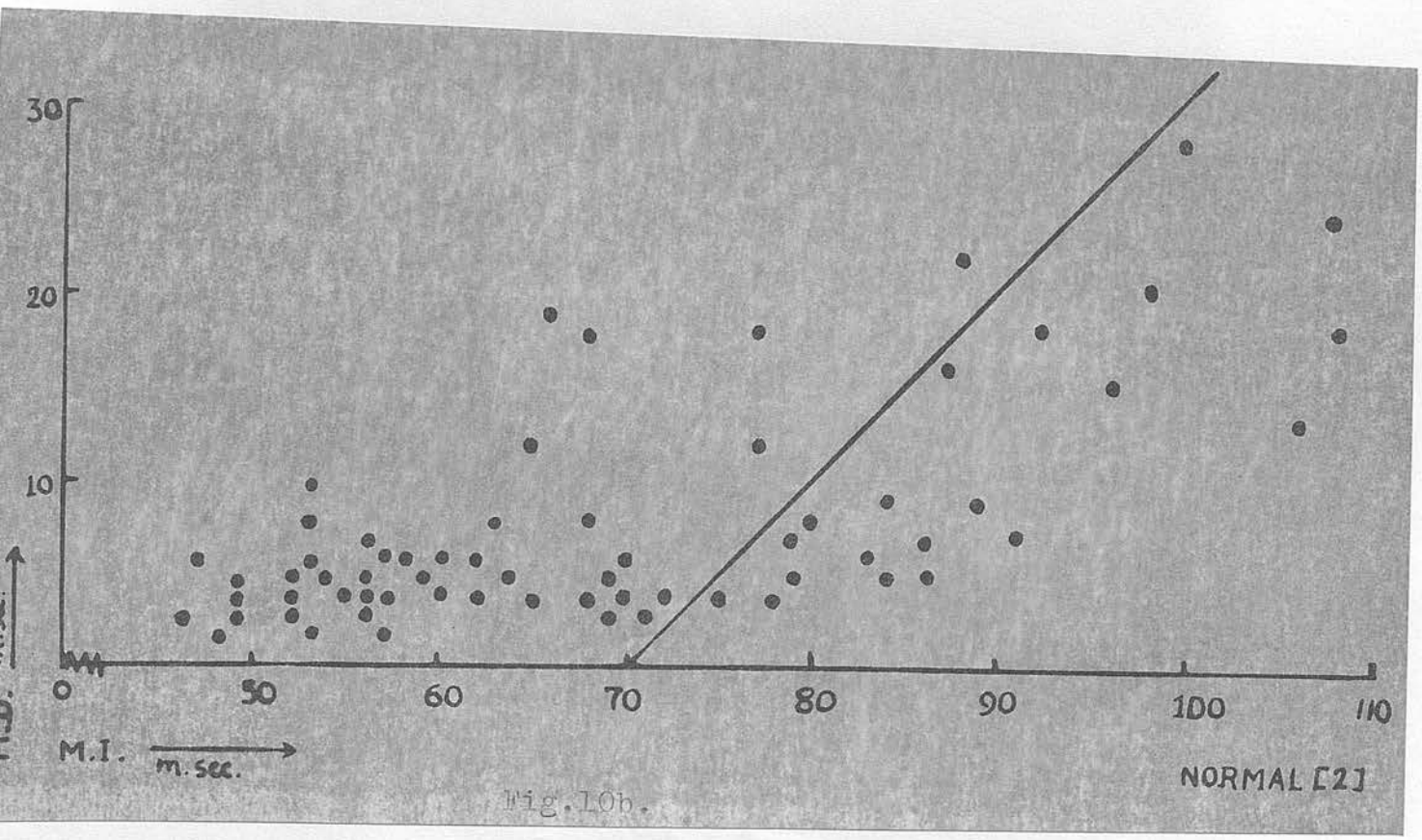


Fig.10b.

CHAPTER 5

RESULTS

1. NORMAL SUBJECTS

Two curves representative of those found in all normal controls are charted in figs. 10 (a and b). It will be seen that with the different loads used, the MI /MD points for many NMUs isolated in one muscle are not arranged along any one or two particular curves as is claimed by Tokizane, but are randomly distributed for values of MI exceeding 70 msec. The MI lies between 55 and 100 msec. for most of the NMUs, representing firing rates of 10 to 18 per second. It is true that the variability (MD) is least when the firing frequency is high, but on the whole the MI/MD curves do not follow a definite pattern and there is no obvious tendency for points to group into a distinct curve of either type.

If a line is drawn at an angle of 45° from 70 msec. on the abscissa, the NMUs in the present experiments will be seen to be arranged on either side of this line, at the standard loads used (fig. 10b). This line is not entirely an arbitrary one. When it was found repeatedly that Tokizane's claim about the presence of two distinct curves could not be confirmed in the present series, Tokizane's original $\bar{\tau}$-S curve (fig. 7) was re-examined. Fig. 11 shows that in his curve also the NMUs are arranged symmetrically on either side of this line, the points along the so-called 'K' curve being arranged on the left and those along 'T' curve on the right. But the clear space

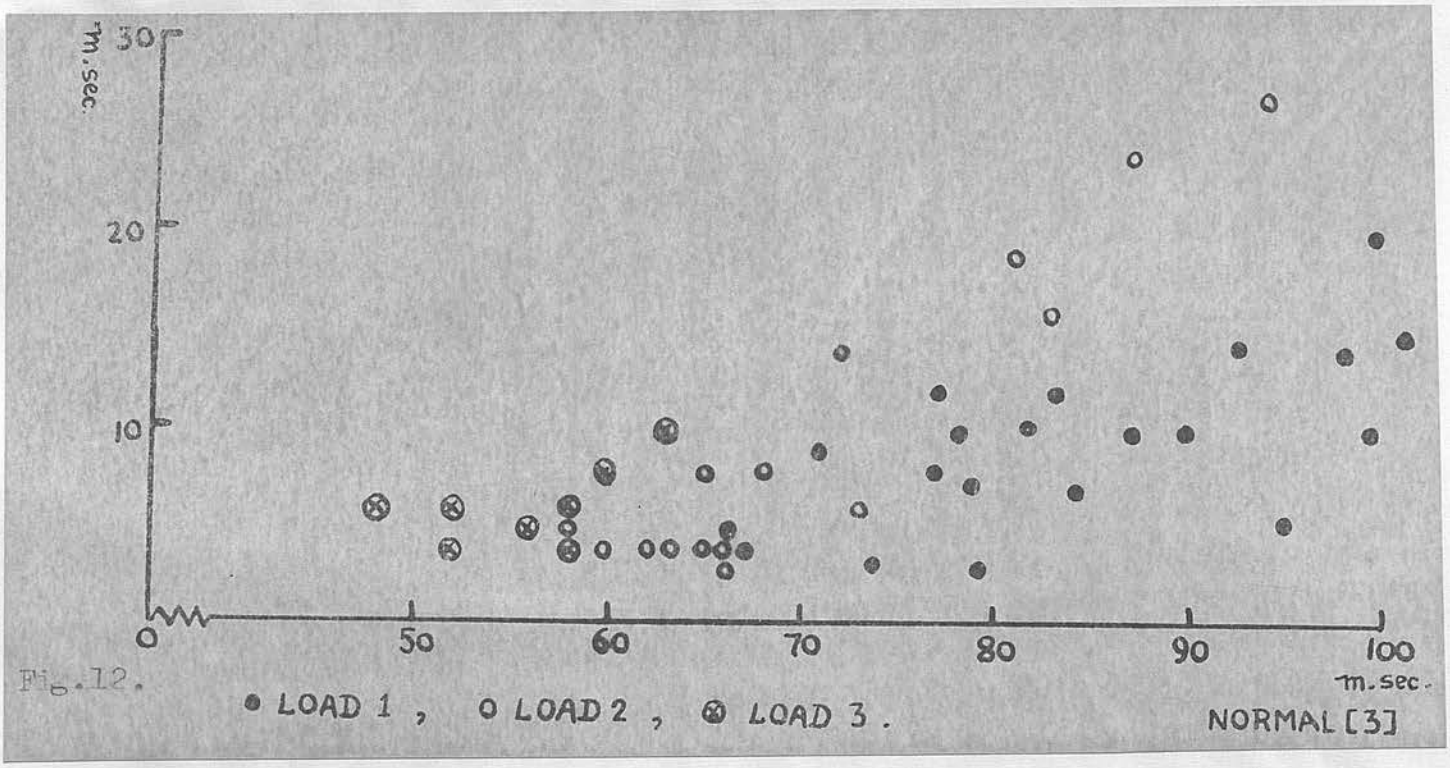
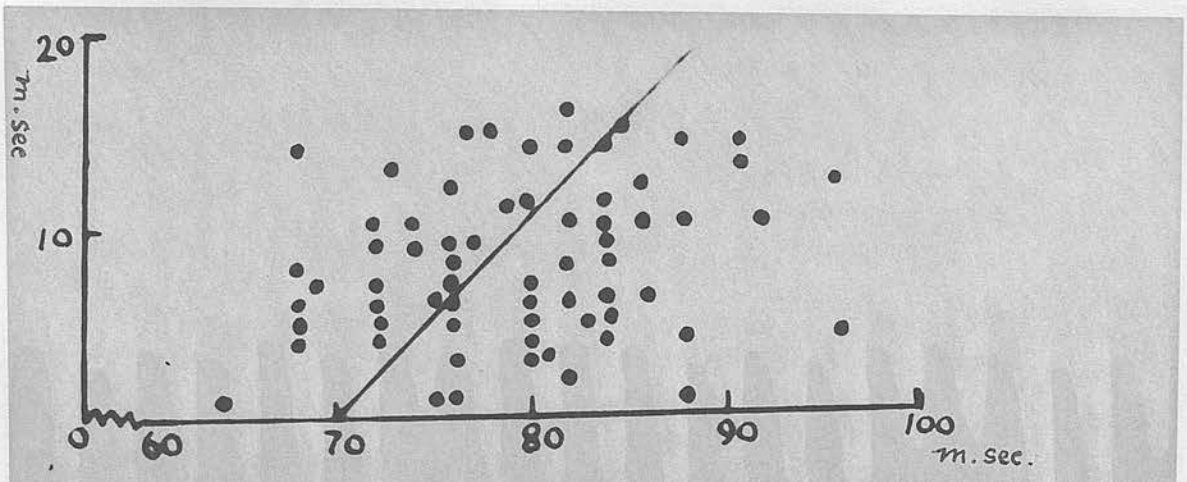
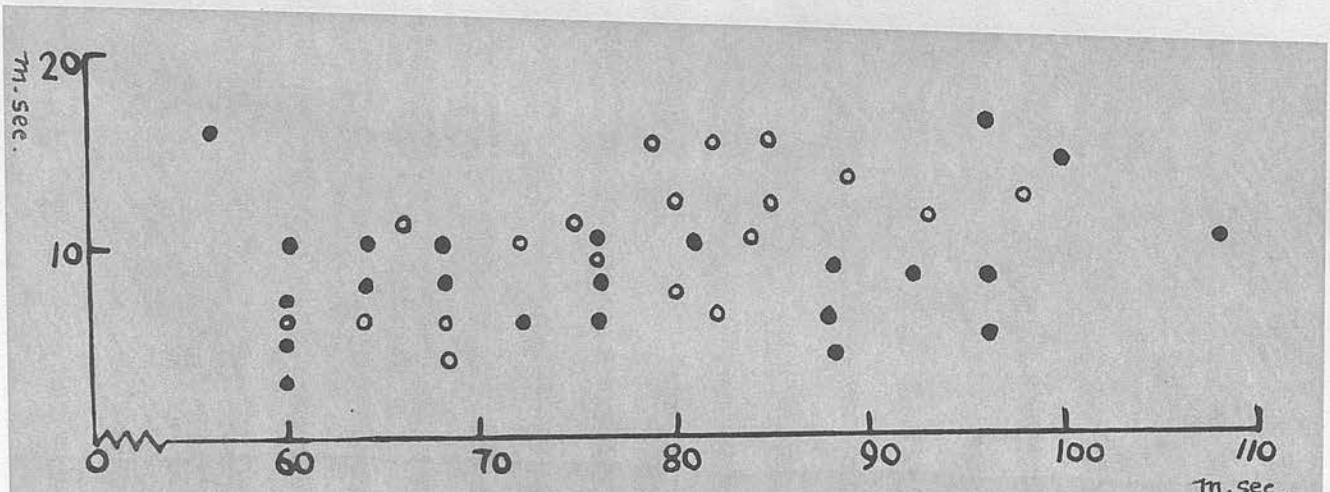

m.sec.
30
20
10
0
50
60
70
80
90
100
m.sec.
• LOAD 1 , o LOAD 2 , ⊗ LOAD 3 .
NORMAL [3]

Fig. 12.



NORMAL: DIFFERENT STRATA [1].

Fig.13.



○ SUPERFICIAL.

● DEEP.

NORMAL : DIFFERENT STRATA [2].

Fig.14.

between the two groups of points which appears in his illustration is entirely lacking in the present series.

The failure to identify two populations may conceivably be due to my selection of a muscle with predominance of one type of motor unit. As a small muscle of hand was used which has wide representation in the motor cortex, the K-type unit should predominate if Tokizane is right. Inspection of figs. 10 (a and b) shows that not only are the NMUs arranged equally on either side of the line which differentiates Tokizane's types, but by simply increasing the load the curve changed. The firing frequency increased as expected, but it was surprising to find that the rate at which variability decreased was faster with increasing load, causing a shift of all NMUs to the left (fig. 12).

FUNCTIONAL ORGANISATION OF MOTOR UNITS IN DIFFERENT STRATA OF THE SAME MUSCLE

To examine this question, biceps brachii was selected as an experimental muscle. The isometric tension for different experiments was kept at a constant and standard level as far as practicable by keeping the angle of flexion of the unsupported elbow constant. The tip of the micro-electrode was first placed within the superficial fibres of the muscle and it was pushed into a deeper part of the muscle after a satisfactory record from the superficial part was obtained. Fig. 13 shows one such analysis which in fact represents the firing characteristics of many different motor units isolated one at a time from different planes of the same muscle. Their individual position is not shown in the chart as the argument

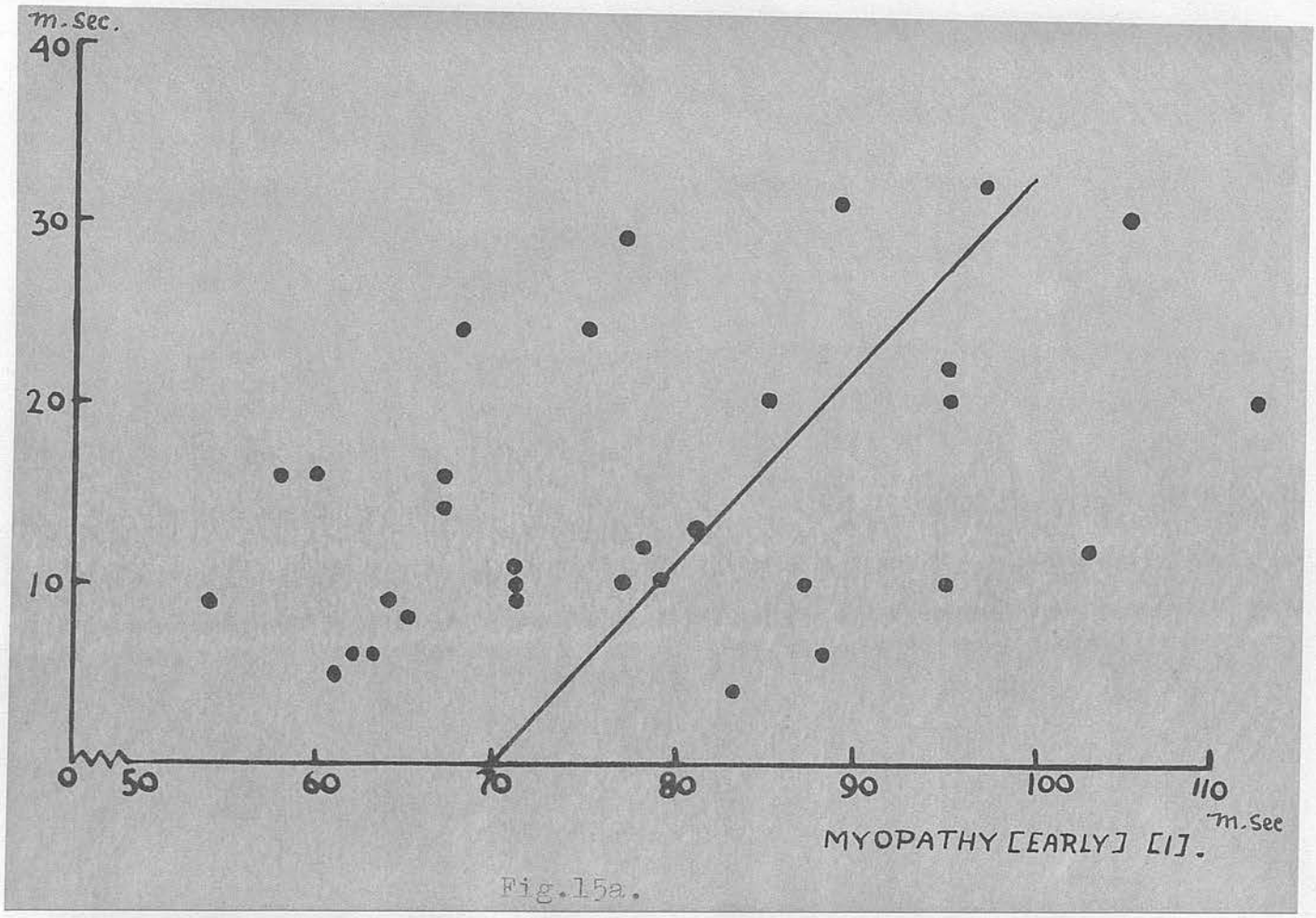


Fig.15a.

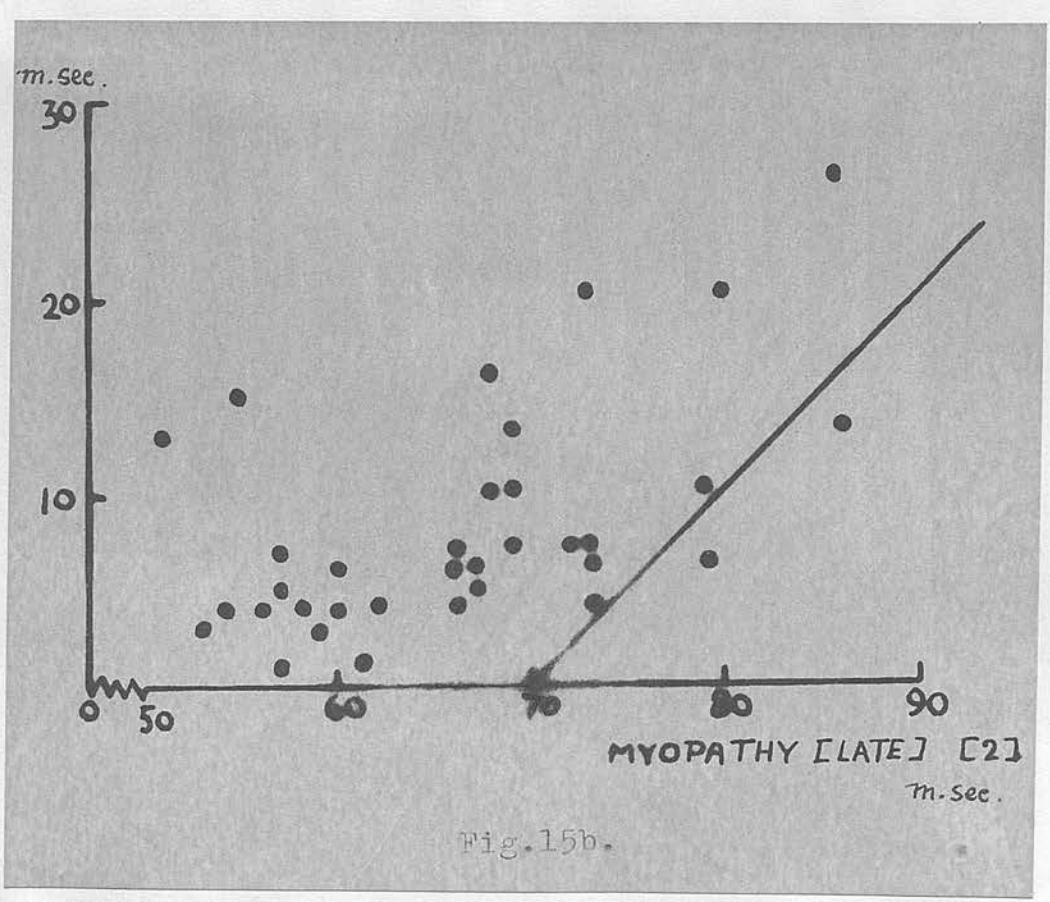
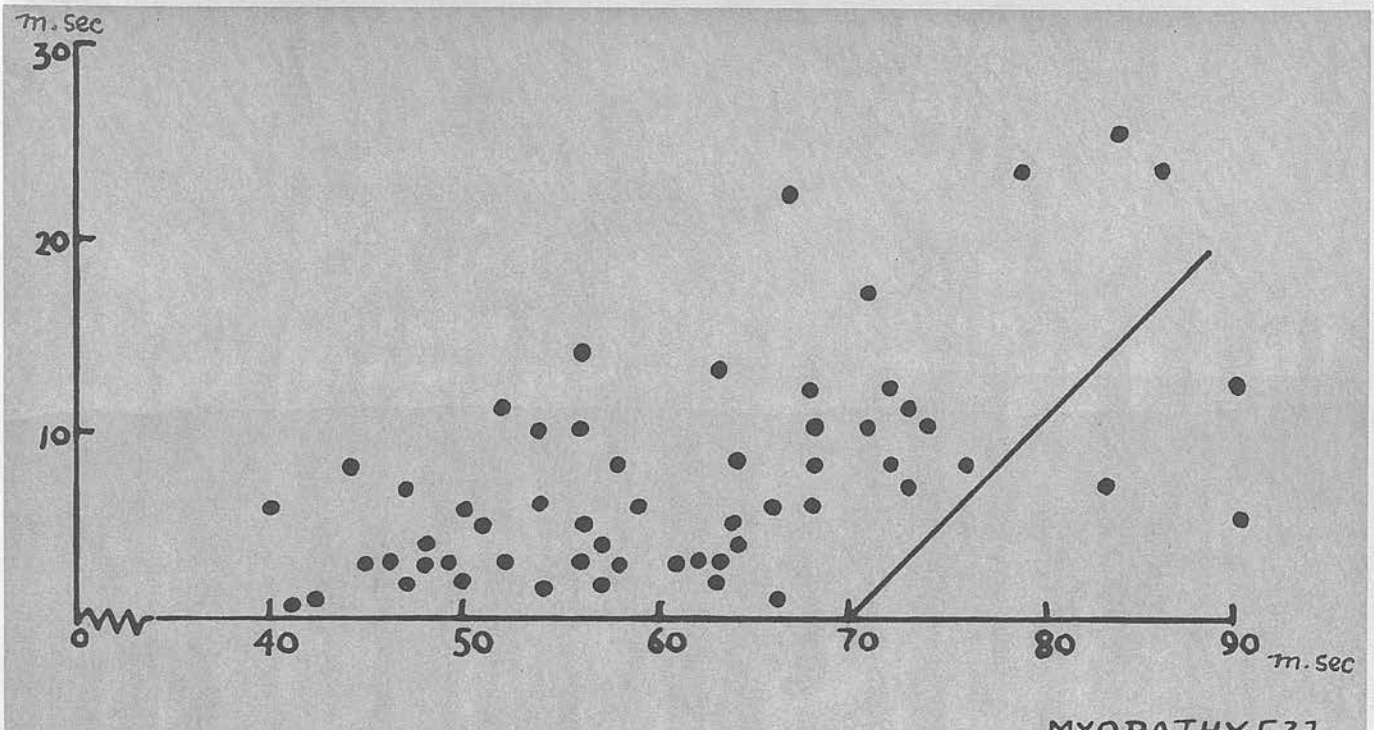


Fig.15b.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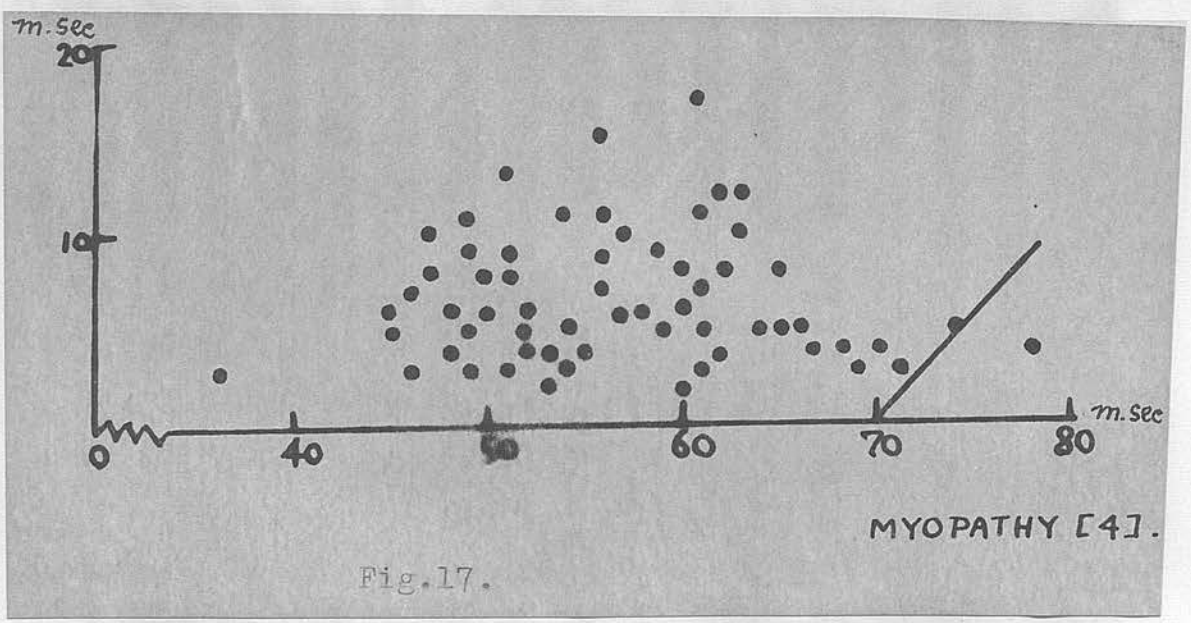
MYOPATHY [3].

Fig.16.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MYOPATHY [4].

Fig.17.

is on statistical grounds, but fig. 14 shows the behaviour of two different units, one from the superficial and the other from the deeper part of the same muscle. As can be seen, there is no speciality in their distribution on the MĪ/MD plot.

2. WEAK MUSCLES

(a) MYOGENIC

The results of similar observations made on a patient suffering from muscular dystrophy are shown in figs. 15 (a and b) which are representative of the 15 patients examined who had different types of myopathy. The records analysed in figs. 15 (a and b) were taken from the same patient using the same muscle but at two different times, 'b' being taken 9 months after 'a'. There was no clinical affection of the small muscles of the hand and no weakness when 'a' was taken. The MĪ/MD plot at that time shows the same sort of relationship as in normal subjects. The clinical picture changed markedly in the following 9 months and when the observations plotted in fig. 15(b) were made, all the small muscles of the hand were very weak and wasted to such an extent that only Load 1 could be used. But even with this comparatively small load, the NMUs in fig. 15(b) can be seen to be shifted markedly to the left of the reference line.

The next two figures are drawn also from patients with muscular dystrophy but having different degrees of affection (clinically) of the small muscles of the hand. A patient with slight affection shows a slight shift of the NMUs to the left, (fig. 16), another with severe weakness shows a marked shift of the NMUs to the left (fig. 17). It can be seen that the

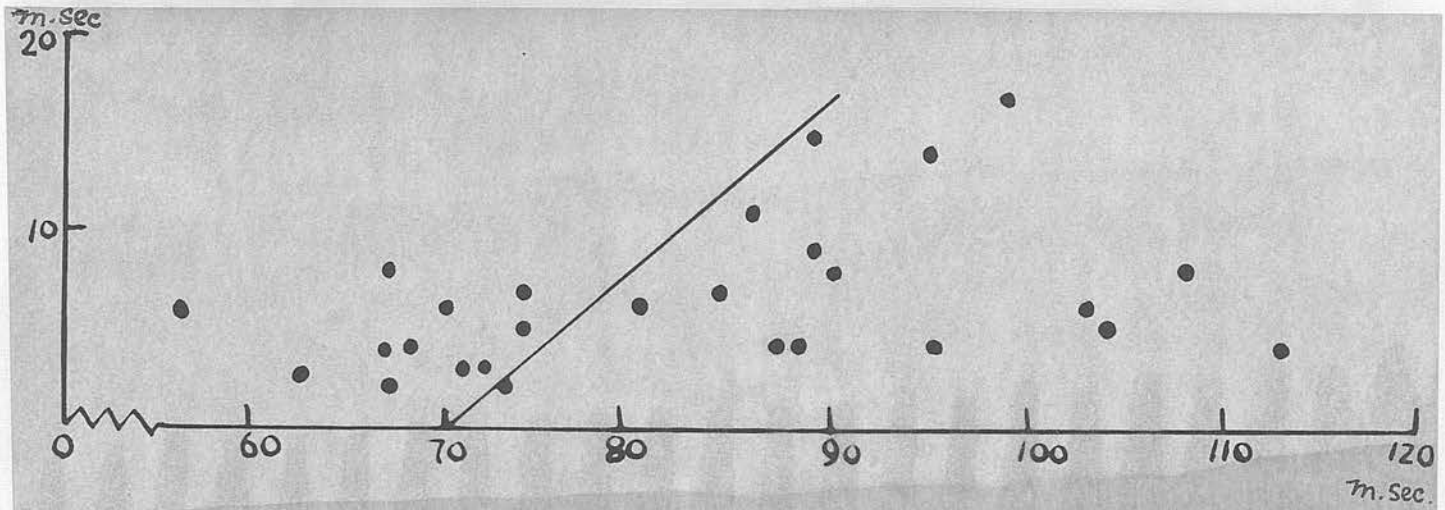

Fig.18. DYSTROPHIA MYOTONICA [1].

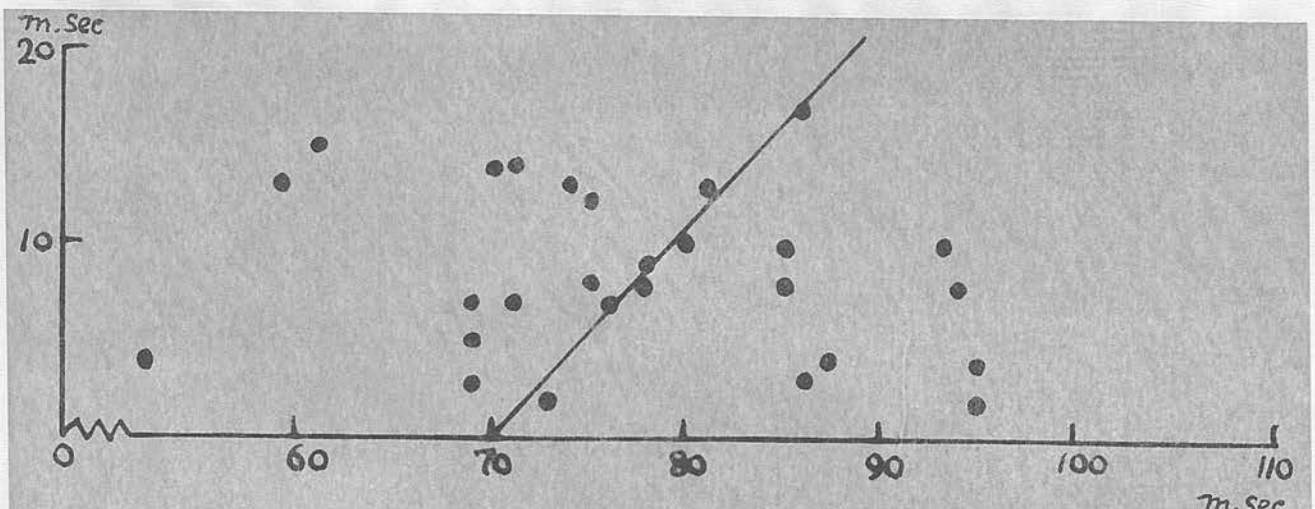

Fig.19. DYSTROPHIA MYOTONICA [2].

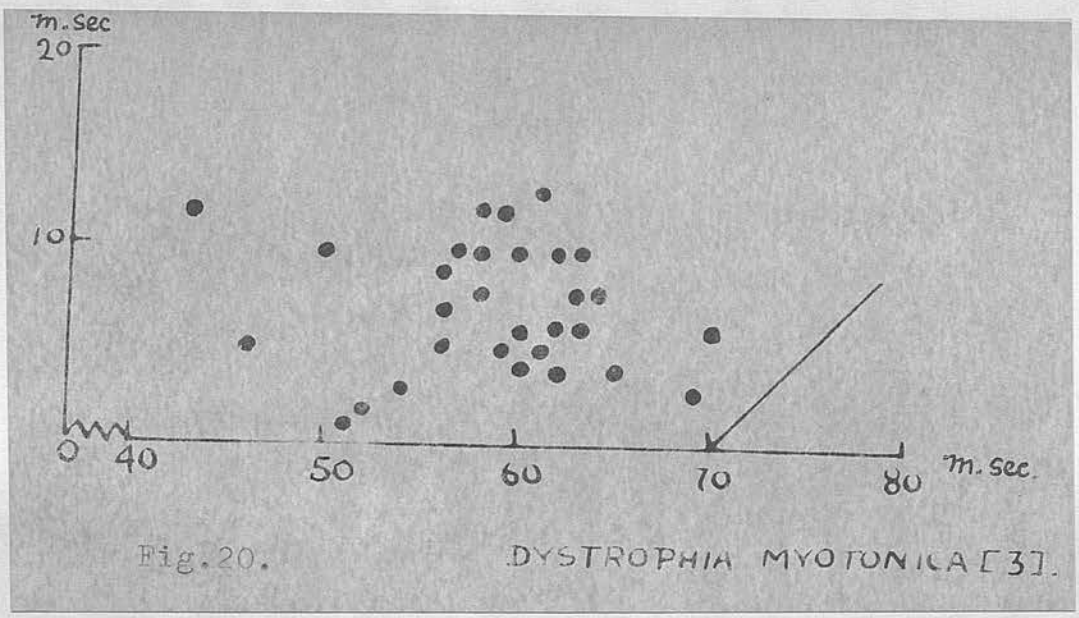

Fig.20. DYSTROPHIA MYOTONICA [3].

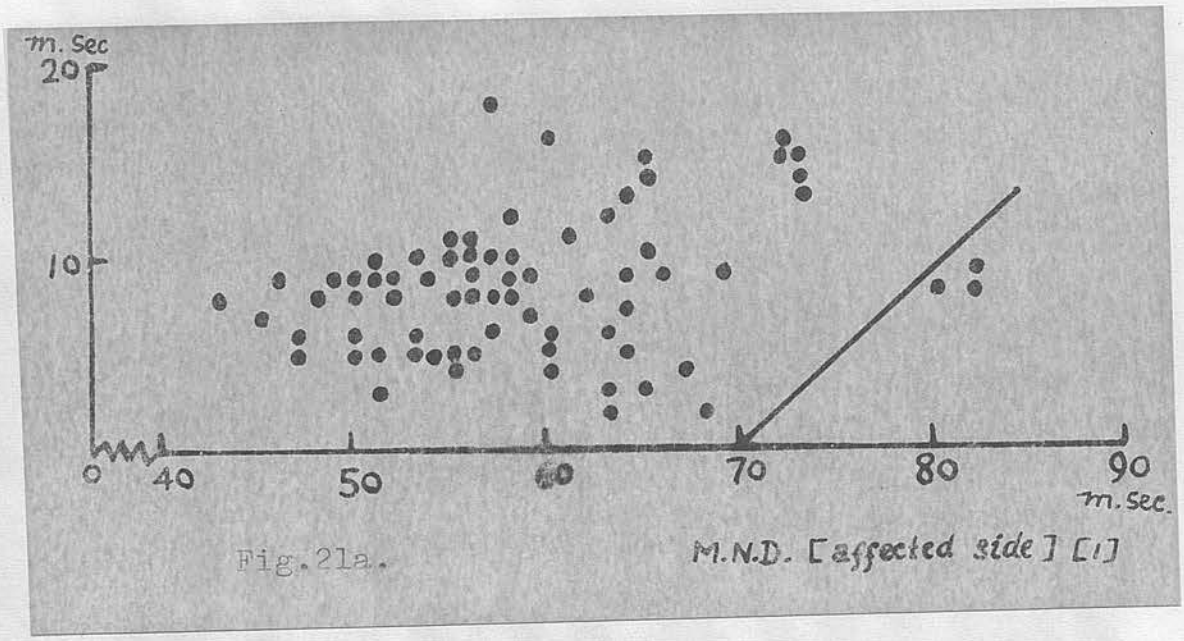

Fig.2la.

M.N.D. [affected side] [1]

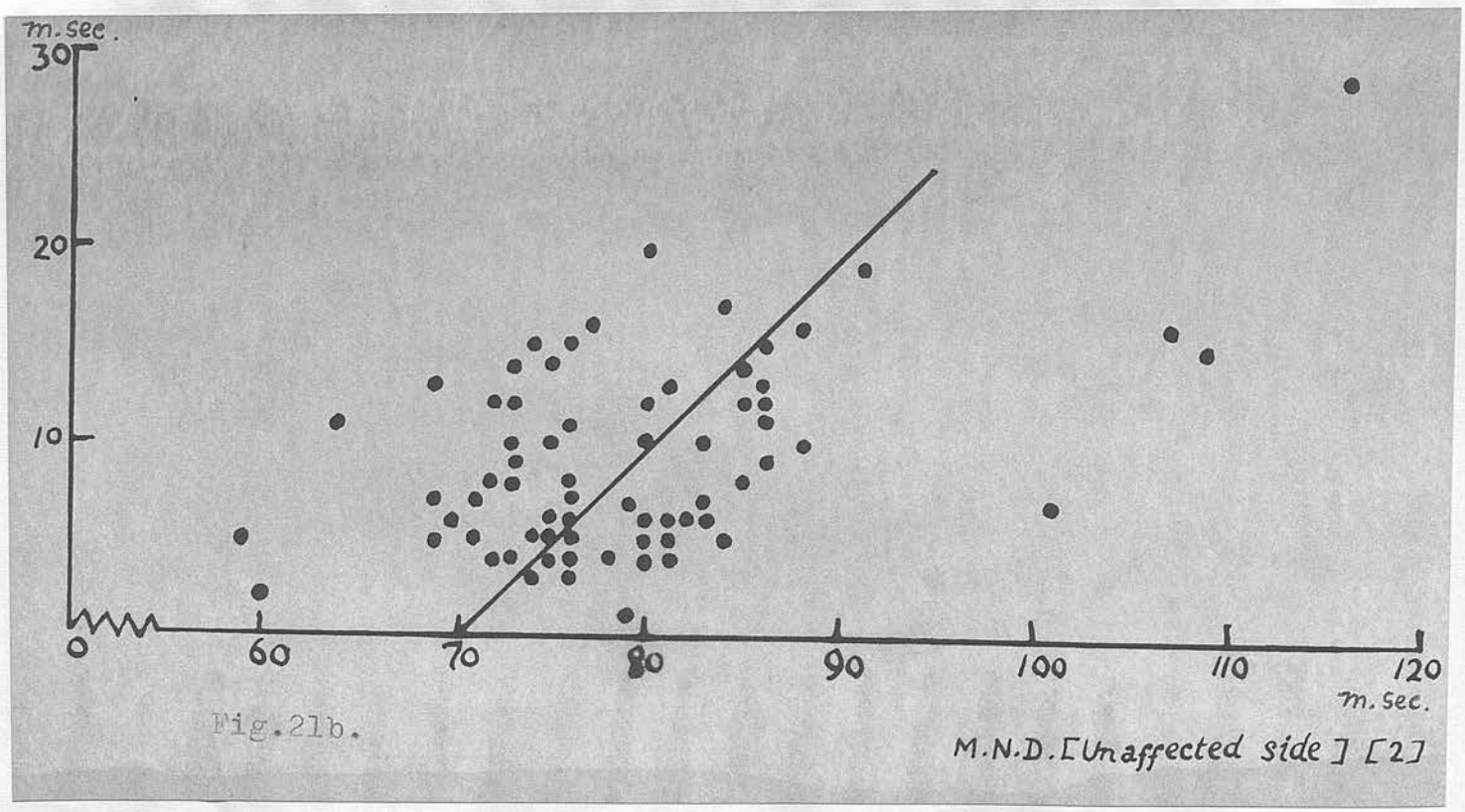

Fig.2lb.

M.N.D. [Unaffected side] [2]

frequency of firing of the motor units increases markedly when using the same or lesser load depending on the degree of affection of the muscles. There is no evidence that a T-type of unit has fallen out leaving K-type units with unchanged MI/MD curves.

The next group of patients selected were all suffering from Dystrophia myotonica, and the present observation is based on 3 experiments on 3 different subjects. Fig. 18 shows the MI/MD plot from a girl of 21 years with no family history of the condition and with no evidence of dystrophy but with myotonia only, of recent onset. The MI/MD chart, using all the three loads shows that the NMUs are distributed within the normal range. Fig. 19 was constituted from data obtained from a woman of 48 years with marked weakness but slight wasting of the small muscles of the hand, and fig. 20 from a man of 22 years with marked myotonia, weakness and wasting. Only Load 1 was used in the last two experiments. It will be seen that there is progressive deviation of the NMUs to the left of the reference line depending on the degree of wasting and weakness.

(b) NEUROGENIC

The first group of 15 patients examined with neurogenic weakness of the small muscles of hand were suffering from Motor neurone disease. Sala (1958) claimed that there was selective loss of T-type ('tonic') units. If he is right, one would expect to see that the NMUs to the right of the reference line disappear in the MI/MD graphs of these patients. Figs. 21 (a and b) show two graphs from the same patient, 'a' being

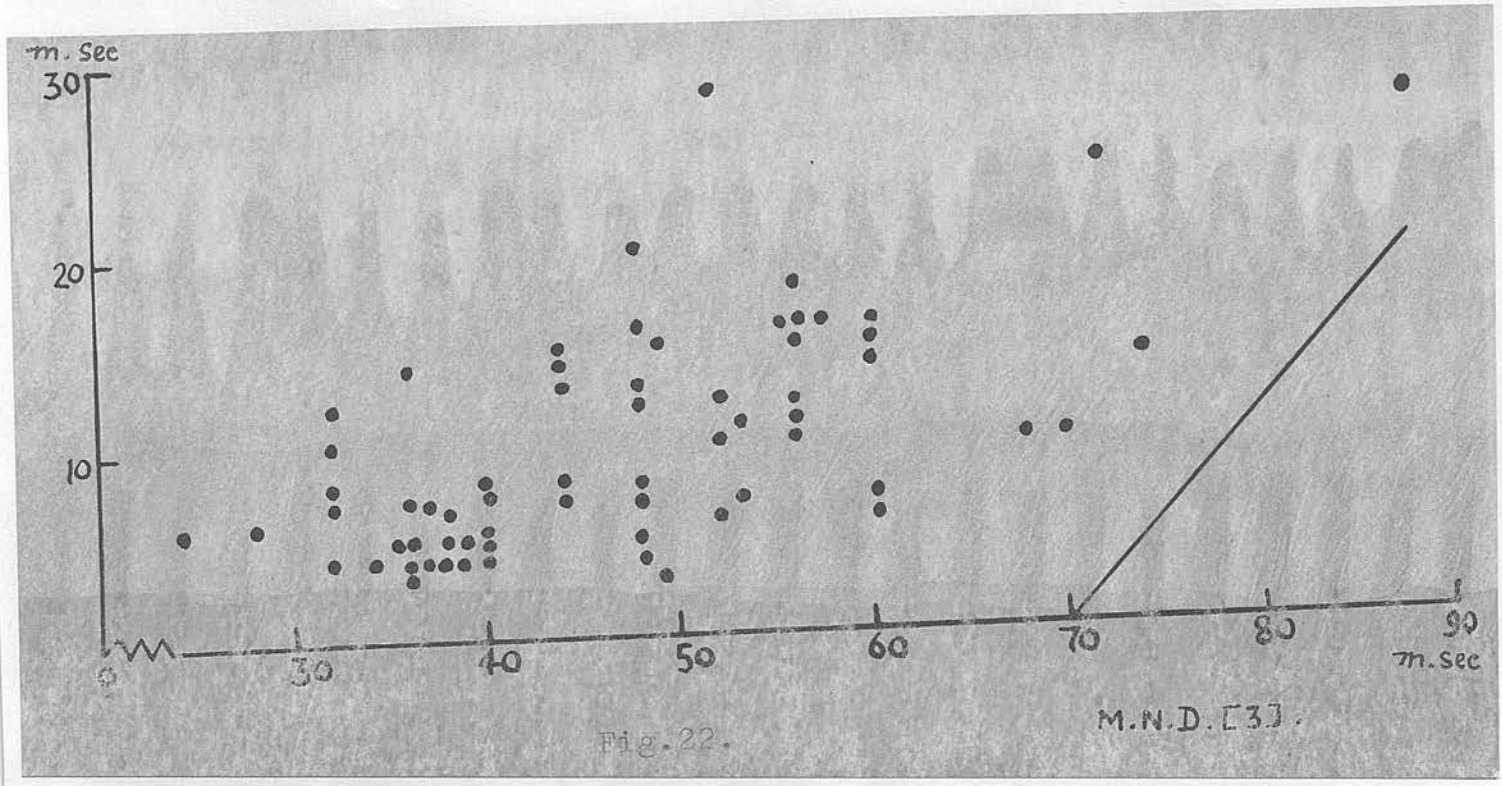
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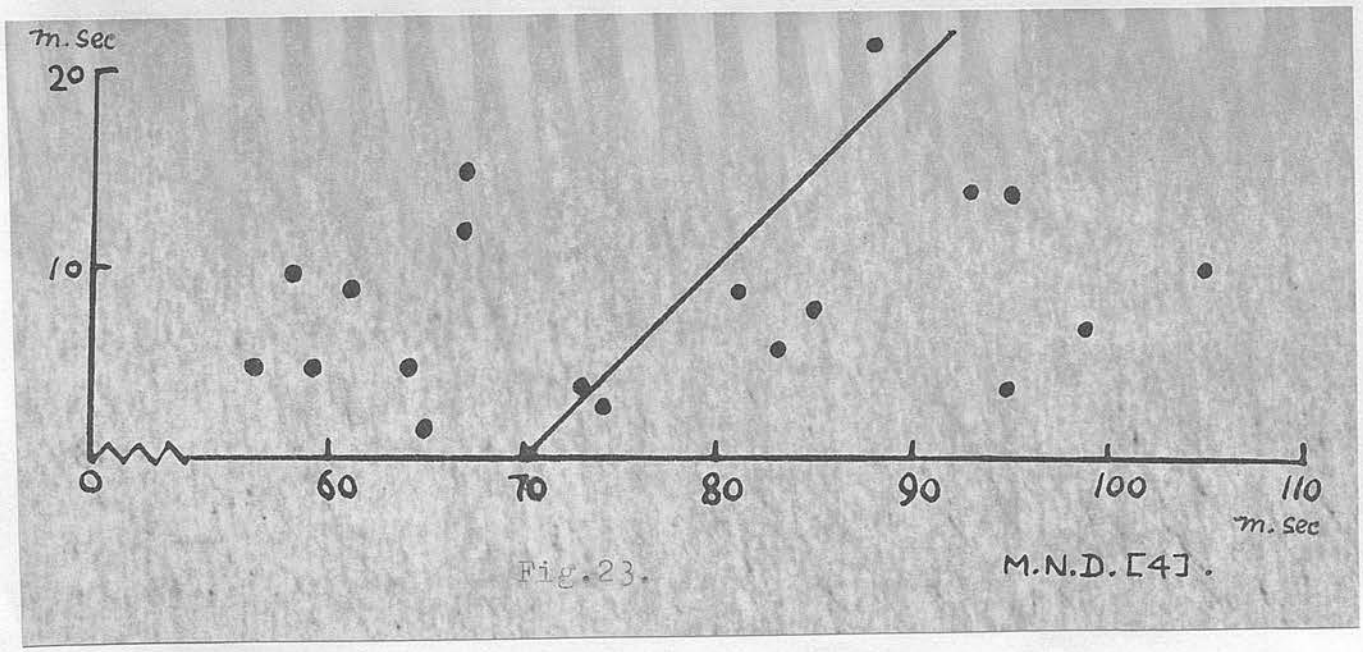
Fig.22.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M.N.D. [4].

Fig.23.

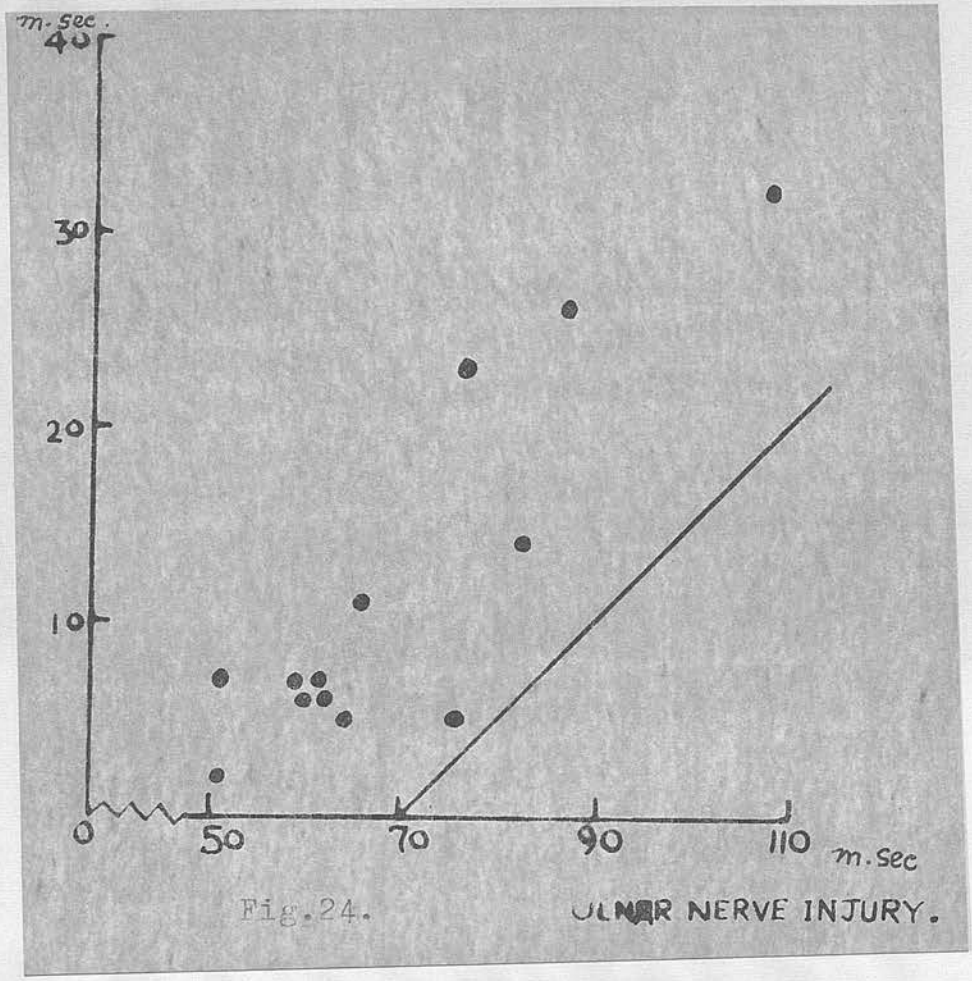


Fig.24. ULNAR NERVE INJURY.

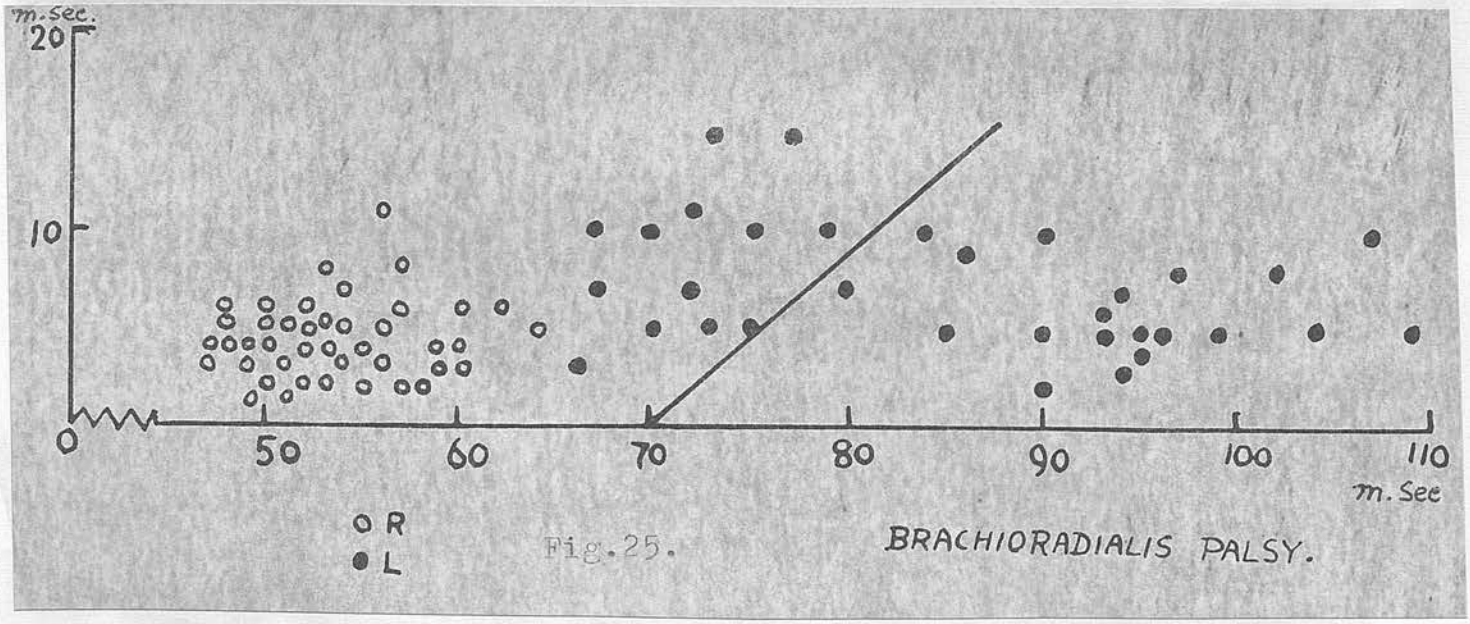
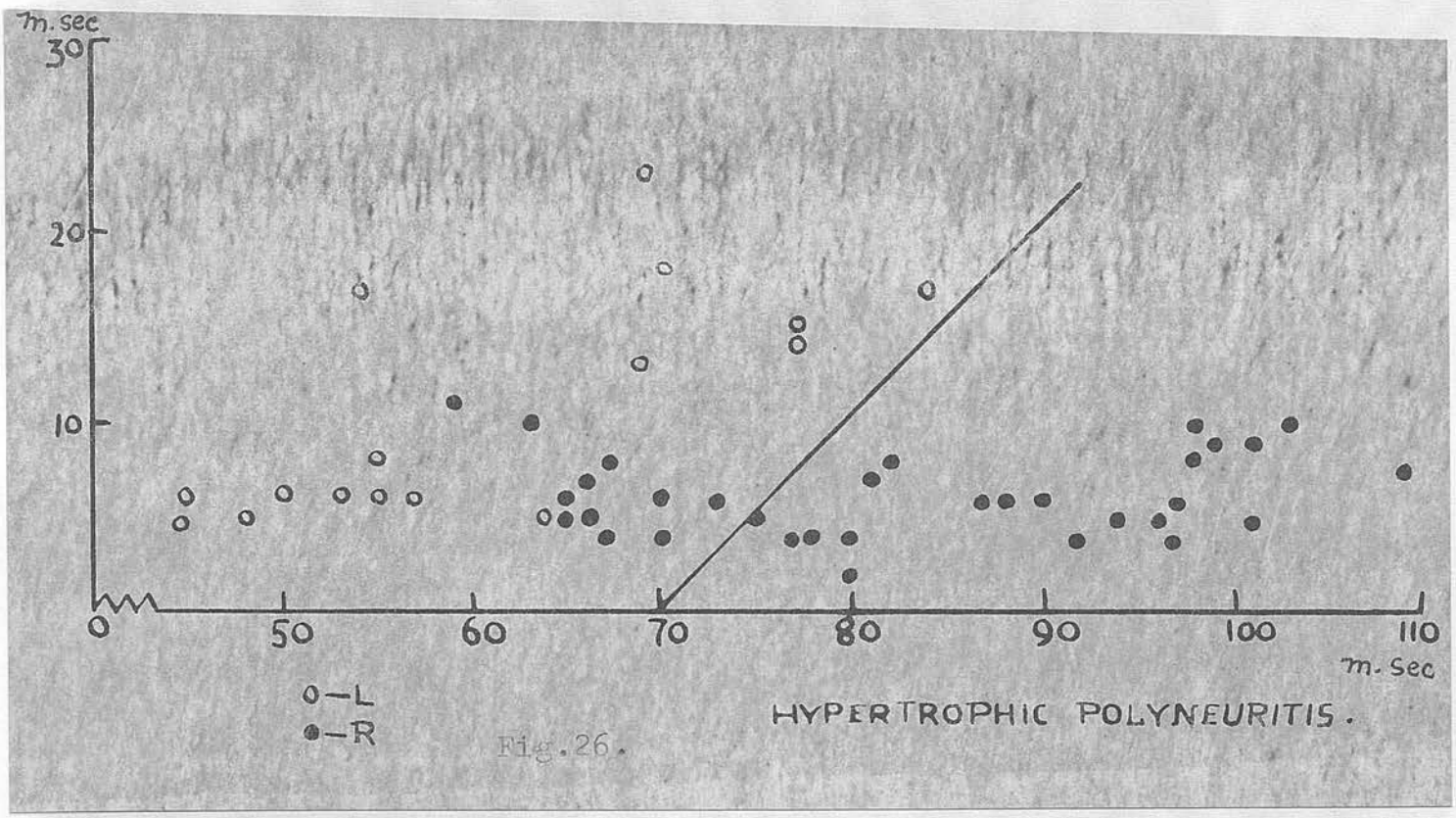


Fig.25. BRACHIORADIALIS PALSY.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HYPERTROPHIC POLYNEURITIS.

Fig. 26.

taken from the affected left (L) first dorsal interosseous muscle, which was markedly wasted and weak (so much so that only Load 1 was used), while 'b' was taken from right (R) first dorsal interosseous muscle which showed no sign of clinical affection (and here all three loads were used). Fig. 21(b) shows a normal distribution of the NMUs, while that from the affected side, using lesser load, shows marked deviation of the NMUs to the left of the reference line. Figs. 22 and 23 show the same feature in two different patients. The former showing a marked shift to the left, was derived from a patient whose muscles were very weak, while the latter, showing normal distribution of the NMU s was from a muscle which was not clinically affected. These findings would not accord with those of Sala (1958), and a different interpretation will be offered.

The next group with neurogenic weak muscles were patients with disorders of peripheral nerves. Fig. 24 shows the results from a male patient of 52 years who injured his ulnar nerve at the elbow and when the record was made his interossei were markedly wasted. The MI/MD curve shows a shift to the left of the NMUs. Fig. 25 was obtained from a patient aged 30 years who had a paretic right brachioradialis muscle (of unknown aetiology) with marked wasting, the left one being normal. Fig. 25 charts results obtained from both brachioradialis muscles, using the same method and the same degree of contraction for both. The MI/MD plot shows a marked shift to the left of the NMUs from the affected side. Fig. 26 represents a similar

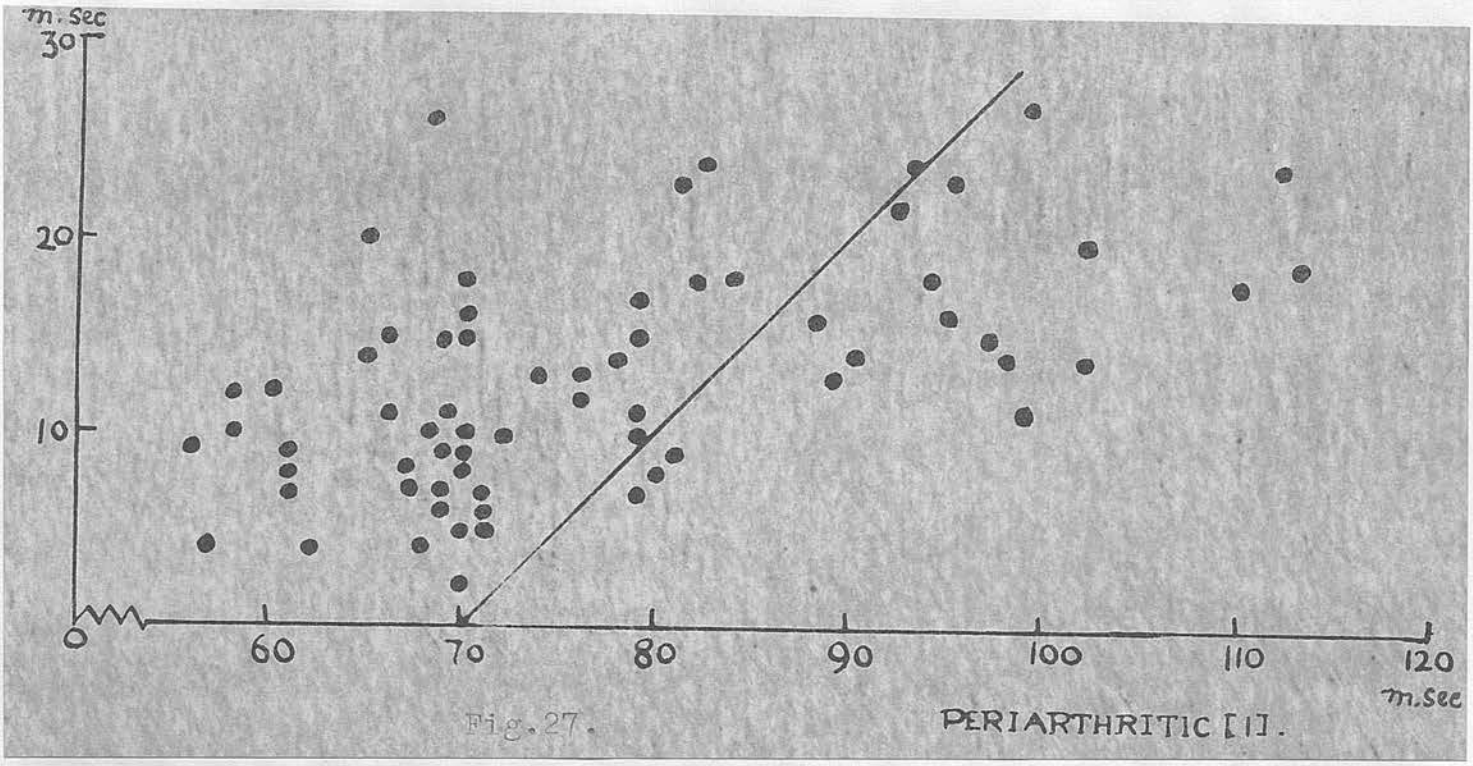


Fig.27. PERIARTHRITIC [1].

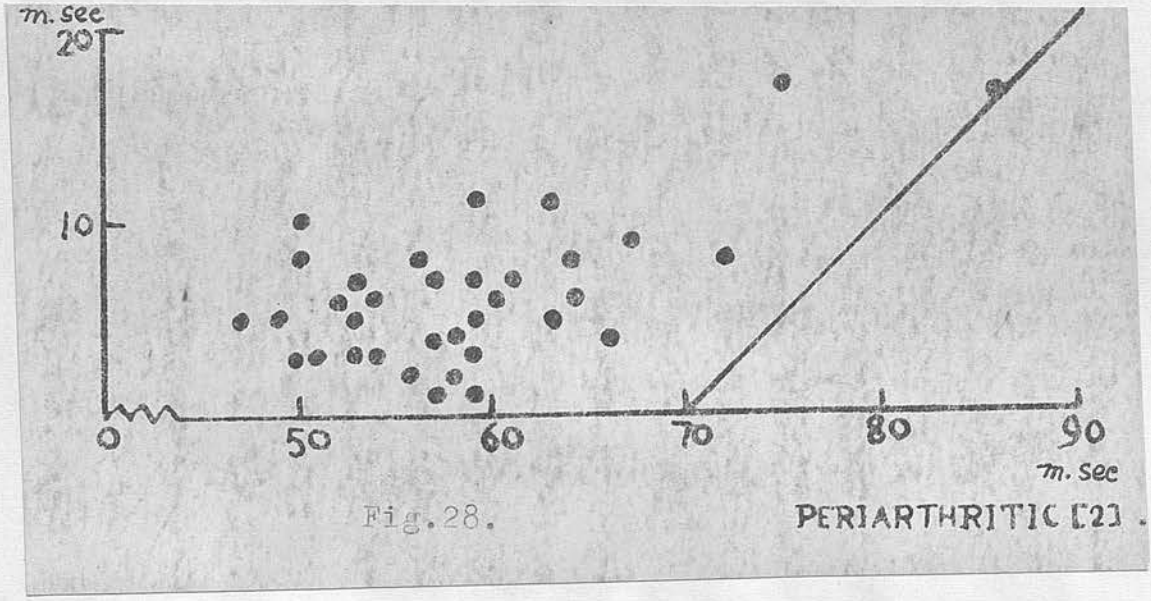


Fig.28. PERIARTHRITIC [2].

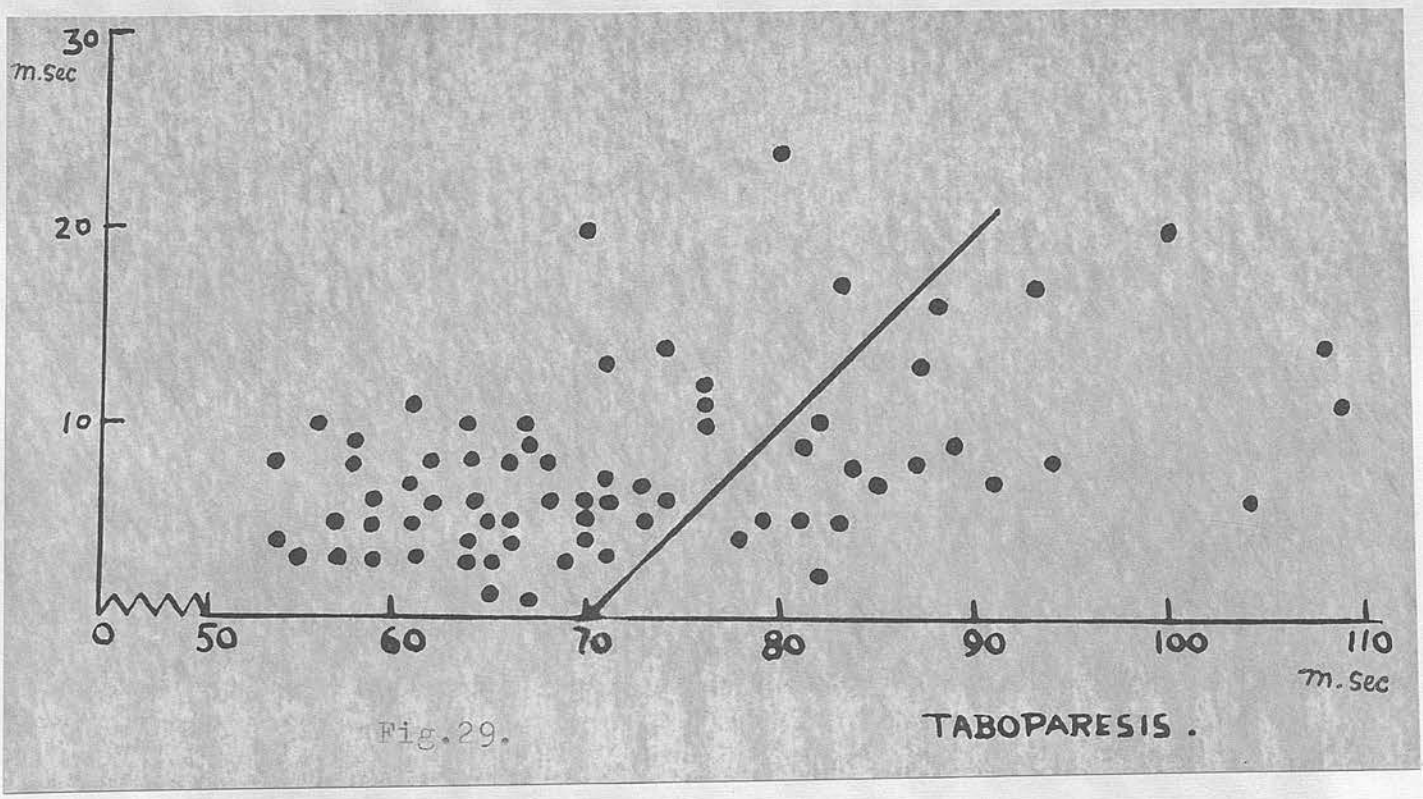


Fig.29.

observation in a man of 61 years who was suffering from hypertrophic polyneuritis. The left ulnar nerve was most severely affected while the small muscles of the right hand were not clinically affected. The figure shows that the NMUs from the affected side are shifted to the left, while those from the right are distributed within the normal range.

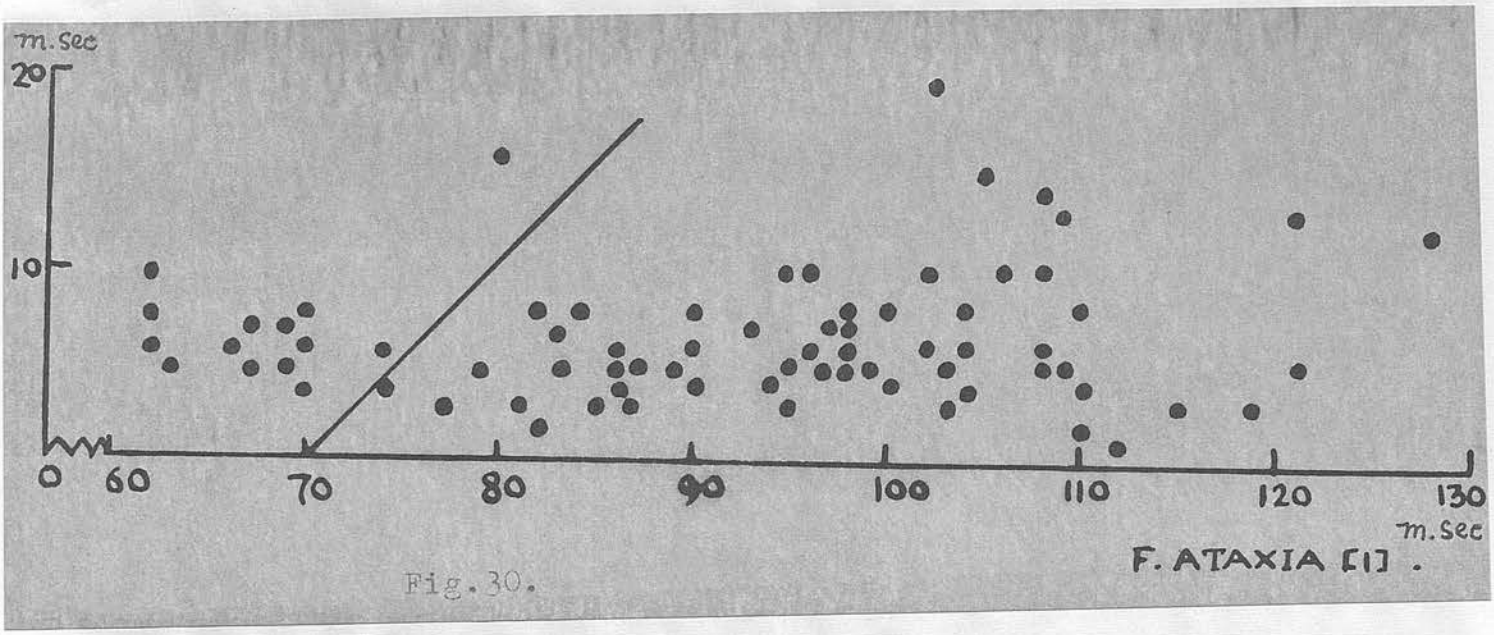
(c) PERIARTHRITIC

Three patients with Rheumatoid arthritis and variable degree of wasting and weakness of the small muscles of hand were examined next. Fig. 27 was prepared from data from a male patient of 60 years with no clinically detectable affection of the small muscles of the hand. Fig. 28 was from a woman of 68 years with marked affection and wasting of all the small muscles of her hands. The fig. 27 shows a normal distribution of the NMUs, while fig. 28 shows a shift to the left.

3. NORMAL POWER WITH ABSENT DEEP REFLEXES

(a) TABES DORSALIS

Three patients with this disease (including one with taboparesis) were examined to see the effect of involvement of the afferent input from the proprioceptors on the MI/MD curve. All these had absolutely normal muscle power with no wasting or any clinical involvement of the small muscles of the hand. Unfortunately, I could not find any patient suffering from this disease who also had wasted small muscles of hand (due to any cause). Fig. 29 shows motor unit behaviour in the first dorsal interosseous muscle of a male patient of 35 years suffering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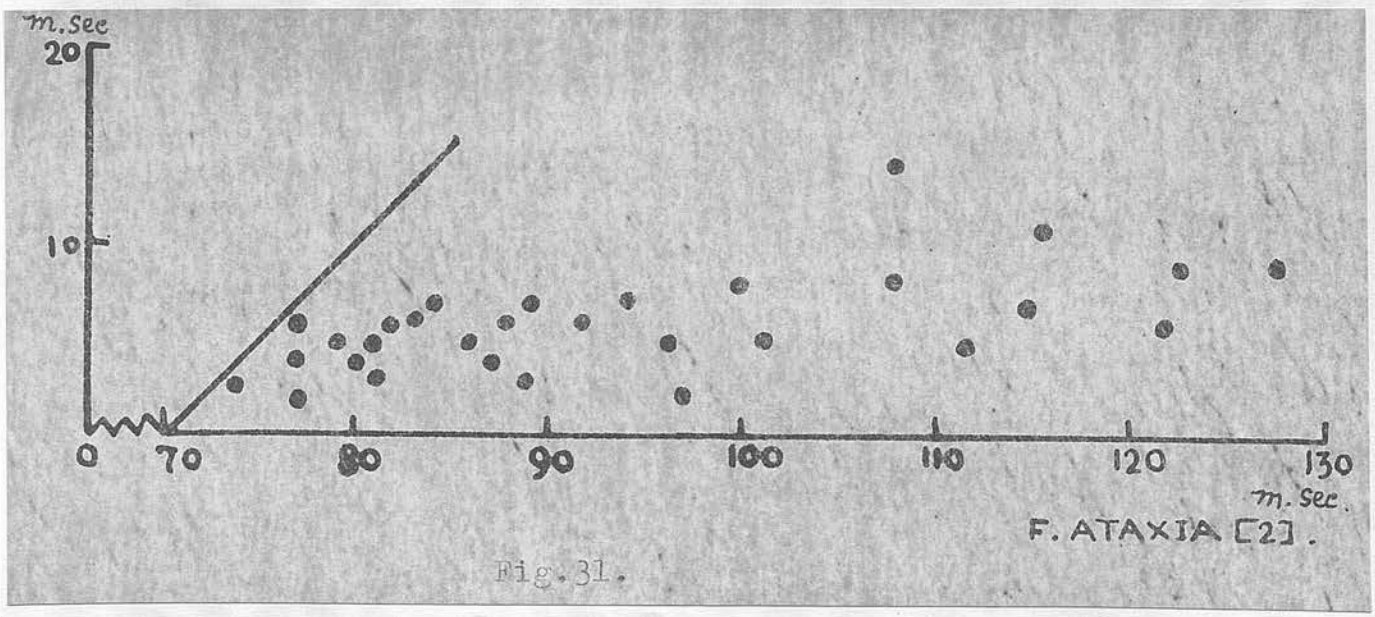
F. ATAXIA [1].

Fig.30.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F. ATAXIA [2].

Fig.31.

from taboparesis. All three loads were used. As can be seen, the scatter of the NMUs is exactly the same as in normal controls.

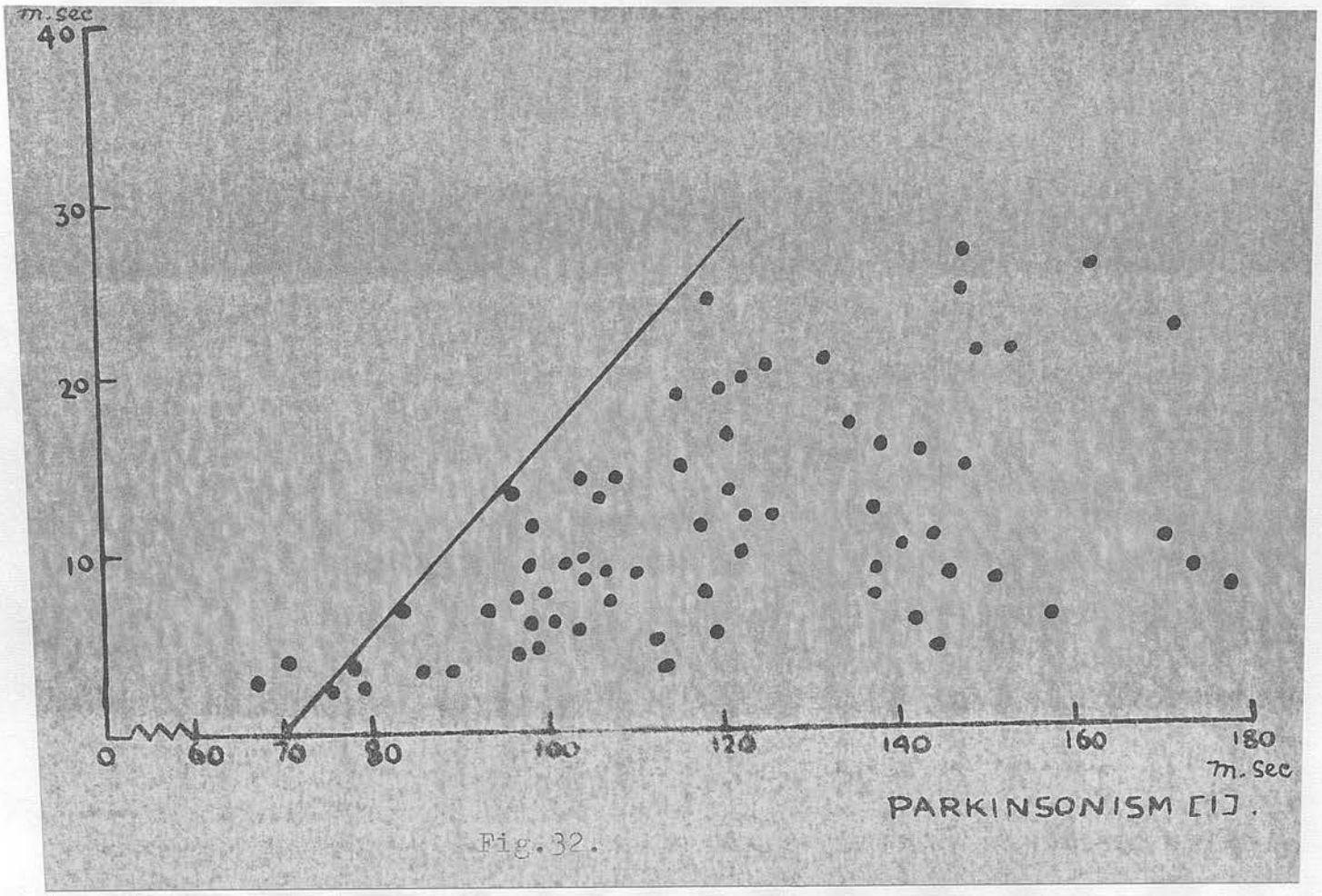
(b) FRIEDREICH'S ATAXIA

Three patients suffering from Friedreich's ataxia were then examined. These patients, did not have any clinical involvement of their peripheral nerves, but all had complete absence of deep reflexes. Levy (1961) has shown, from this laboratory, that the areflexia is probably due to lack of supraspinal facilitation of gamma efferent fibres to muscle spindles and not to abnormality of the peripheral reflex arc.

The small muscles of the hand were perfectly normal in strength and contour in each case (as in the preceding group). The method used (including load) was the same as before. Their MI/MD charts are shown in figs. 30 and 31. Fig. 30 (from a boy of $14\frac{1}{2}$ years) has few points to the left of the reference line. Eighty per cent of the points plotted lie to the right of the reference line, and the mean deviation does not increase significantly until the mean interval is 100 msec. Fig. 31 was taken from a girl of 14 years. In this figure, all MI/MD points are on the right of the reference line and again, there is surprisingly good regulation of firing rhythm at slow rates.

4. PARKINSONIAN RIGIDITY

Thirty patients suffering from Parkinson's disease were then examined. Different types of patients were selected with different degree of involvement of muscles. The muscle investigated was the first dorsal interosseous in each case and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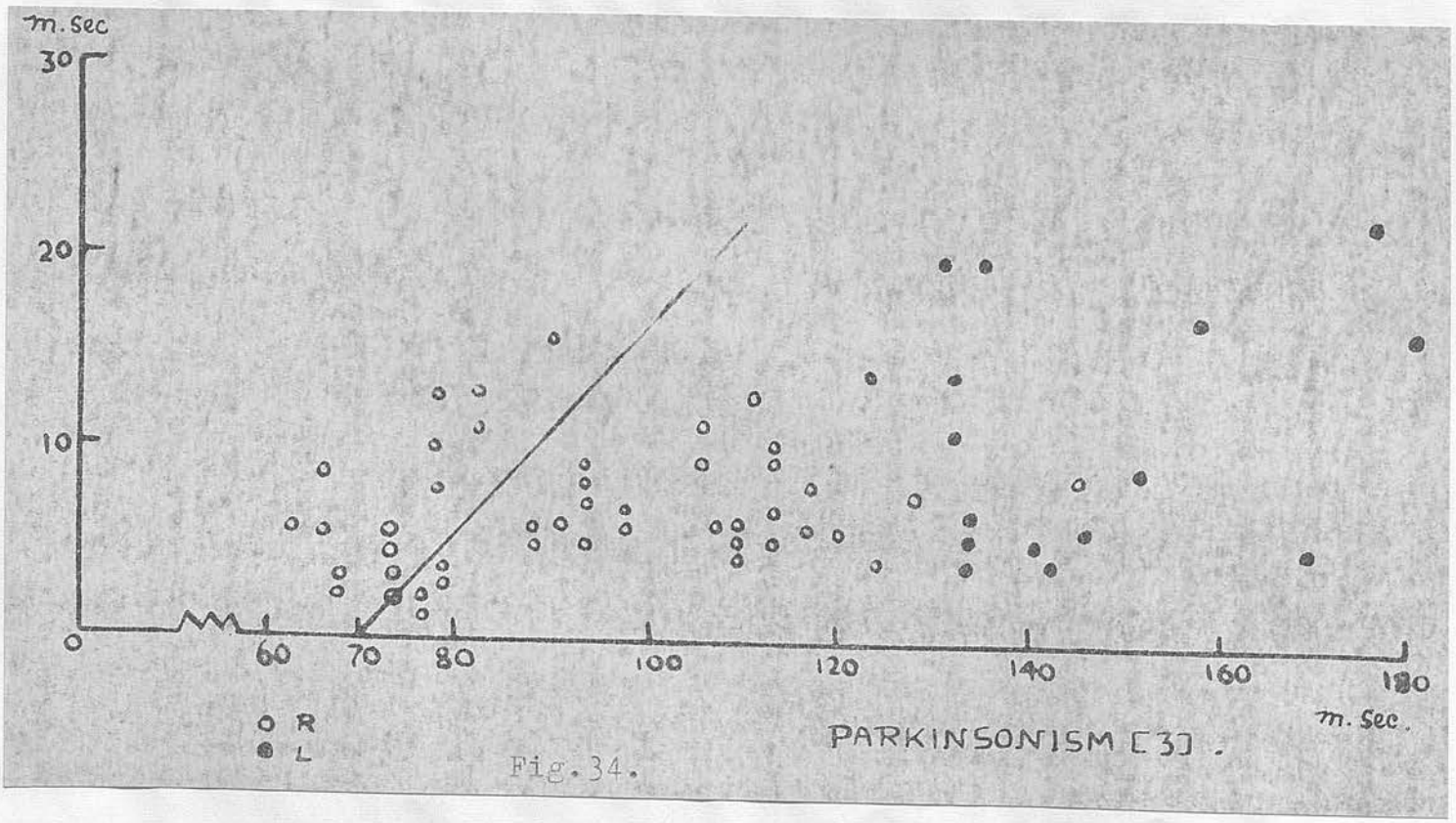
PARKINSONISM [1].

Fig. 32.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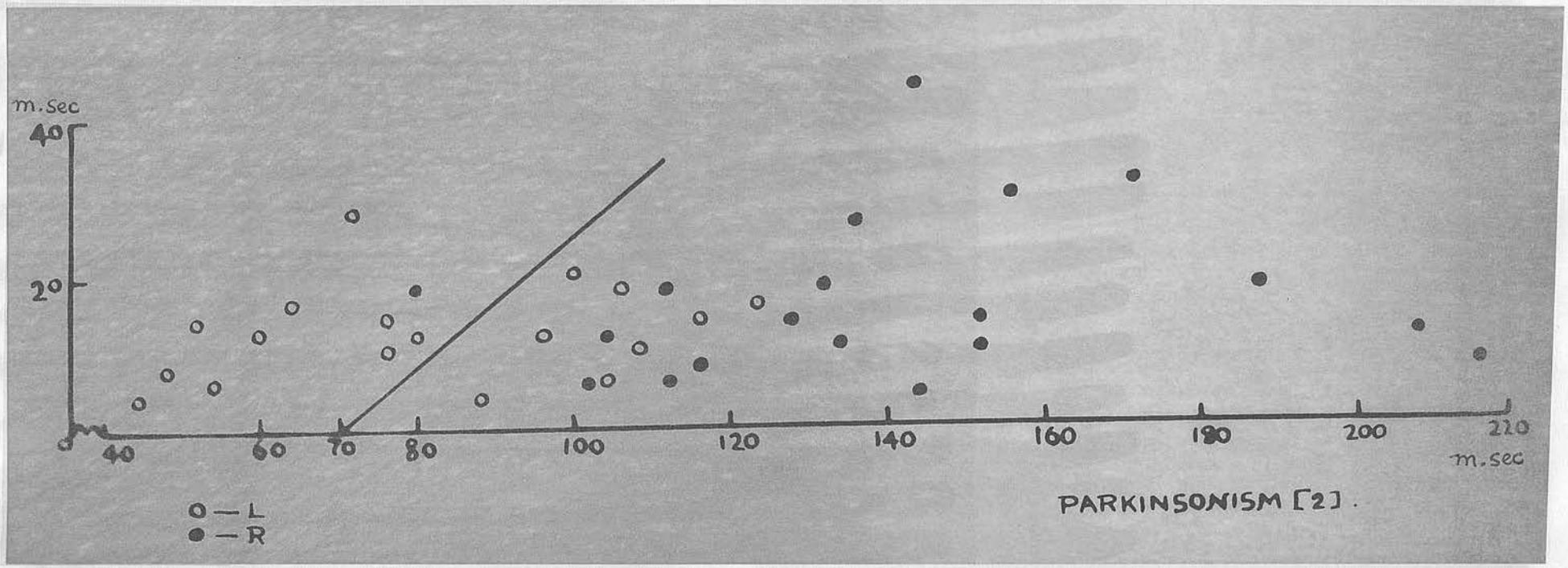
R
L
PARKINSONISM [3].

Fig. 34.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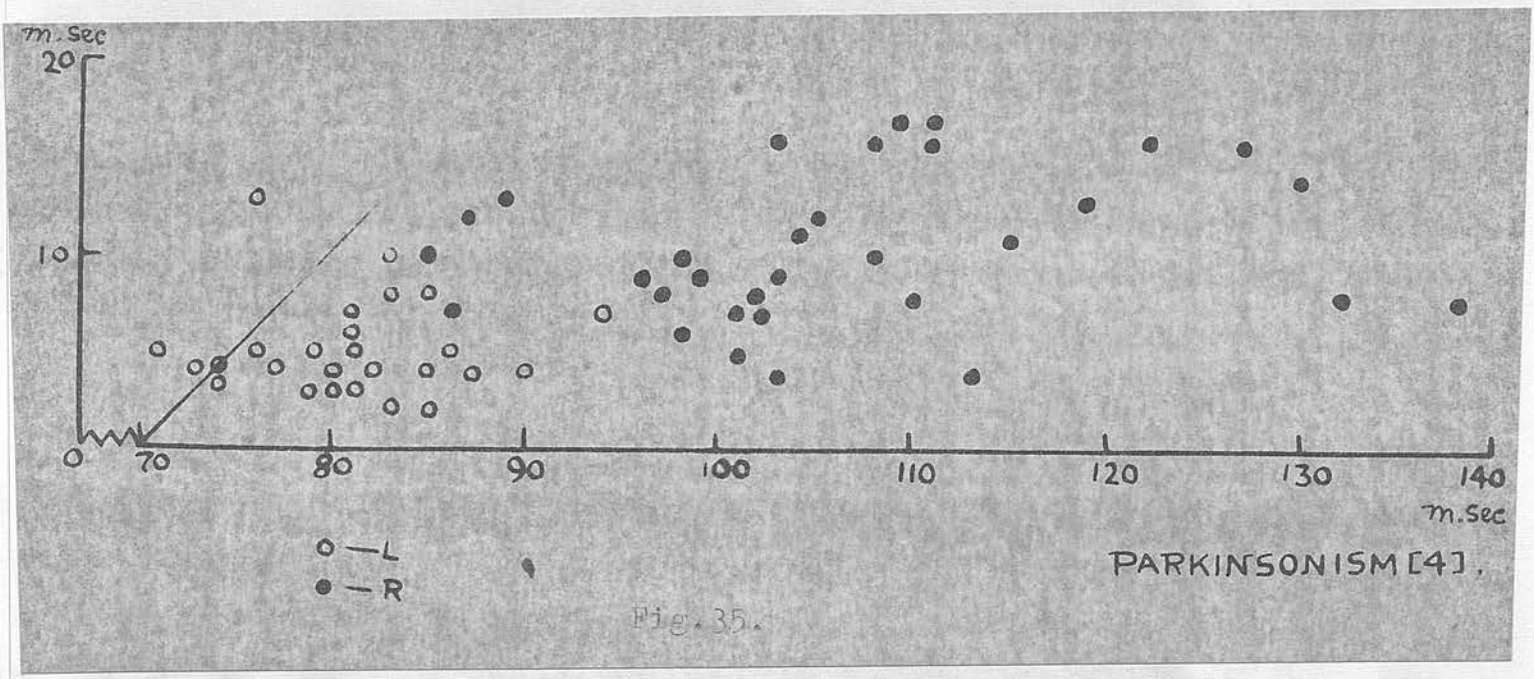
PARKINSONISM [2].

Fig. 33.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PARKINSONISM [4].

Fig. 35.

the loads were the same as in previous experiments. There was no wasting or weakness in the small muscles of the hand in any of these patients, and they all had rigidity with or without tremor as a presenting feature. Fig. 32 shows a typical example from one such patient, who was a woman of 51 years who had had the illness for more than 30 years. The NMUs in her MI/MD curve virtually are on the right of the reference line, in this respect resembling cases of Friedreich's ataxia, and as in that condition, there is a definite shift to the right. Fig. 33 further illustrates this point. It is constructed with data from a male patient of 59 years who had unilateral Parkinsonism for many years affecting the right side of his body. The MI/MD chart from the left hand shows a normal distribution of the NMUs, but those from the affected side are definitely shifted to the right. Figs. 34 and 35 are prepared from patients with bilateral Parkinsonism, but the rigidity was asymmetrical. The data in fig. 34 were obtained from a male patient of 55 years who had only 'unsteadiness' on the right side for one year, but tremor and rigidity on the left side for 4 years. The figure shows a remarkable difference in the behaviour of the NMUs from the two sides. The same difference between the two hands can also be seen in fig. 35 which was obtained from a woman of 68 years who had gradually increasing stiffness on the right side for years, but stiffness on the left side only a few weeks before the record was taken. Clinically, cogwheel rigidity was present bilaterally but much less marked on the left side. Here also the difference in the

behaviour pattern from the two sides can easily be seen. In all these pictures it is obvious that the NMUs from the affected side are not simply arranged along or around the so-called T-curve, but in fact are arranged haphazardly on the right of the reference line. There are quite a few NMUs in the MI/MD plots of these patients with MI significantly greater than the normal maximum, i.e. there is a definite shift to the right. In other words, there are an unusual number of motor units with a firing frequency much lower than observed in normal subjects, yet the variability of these slowly firing units is surprisingly low. To some extent there is a correlation between the degree of rigidity and the retardation of firing rate.

CHAPTER 6

ANALYSIS OF RESULTS

It is clear from the experiments reported in the last Chapter that so far as muscles of the upper limb are concerned, there are no clear and distinct curves in normal subjects with a horizontal part and then an upward inclination. The NMUs in the normal subjects are not arranged along any definite curve. Their firing frequency varies from 10 to 18 per second on average at the range of loads used. It was found possible to shift the NMUs from one side of the graph to the other by simply increasing the load (fig. 12).

The mean deviation of the firing interval at steady tensions or changing tension does not remain constant but it does not alter in any predictable way. For instance, it does not decrease steadily as firing rate increases. The relationship between mean firing interval and its mean deviation is not so regular as to cause the plotted points to fall into the distinct and different 'K' and 'T' curves of Tokizane.

A line drawn from MI = 70 msec. with zero deviation at 45° from the abscissa clearly separates the two curves described by Tokizane. The present findings confirm that MI/MD points are scattered fairly symmetrically on each side of this line in normal subjects (at least for the first dorsal interosseous muscle). This can be readily appreciated as the frequency of firing of motor units, in these experiments, varied from 10 to 18 per second (mode = 14/sec), i.e. with a modal MI of about 70 msec. Their variability was unpredictable since they were

found to be arranged irregularly on either side of the reference line until MI $\leqslant$ 60 msec. when (in agreement with Tokizane) the firing pattern became more regular.

Tokizane's hypothesis on the functional organisation does not fit the observations recorded in this study. If his hypothesis were correct, one would have expected to find NMUs from the first dorsal interosseous muscle to be arranged predominantly along the 'K' curve (i.e. to the left of the reference line), the forefinger being capable of quick movement and having a wide representation in area 4 of the motor cortex. No confirmation of this could be found. Shift to the left of the NMUs was only found when the muscles were weak and wasted and this finding was consistent irrespective of the aetiology for wasting.

Tokizane's theory of "corticalization" (where curves with a short horizontal part persist or predominate) and "spinalization" (where curves with a long horizontal part predominate or persist) is unacceptable, as well defined horizontal parts were rarely present in the MI/MD plots and there were certainly no criteria which differentiated one type of unit from another.

It has been demonstrated (figs. 13 and 14) that different strata of the same muscle do not seem to have NMUs with different MI/MD characteristics. This is in conformity with Lindsley (1935) who found that "motor unit responses do not differ significantly from one muscle to another or in different parts of the same muscle". This does not, of course, exclude the possibility that there might be differences in type of fibre in human skeletal muscle at different depths but if there

is any such arrangement it is impossible to recognise it by the method devised by Tokizane.

Tokizane's statement that 'T' units (to the right of the reference line) are selectively lost in tabes dorsalis was not confirmed. My experiments do not rule out or contradict the possibility that the afferent input from the proprioceptors does have a controlling influence on the firing frequency of motor units and indeed this is true (see Chapter 1, B and C). In tabes dorsalis, as in other conditions, the tension developed in the muscles concerned seems to be the governing factor for the firing frequency.

Bergamini (1959) found that most of the MI/MD points fell on the left side of the chart in cases of progressive muscular dystrophy. He interprets this as loss of 'T' units with retention of 'K' units and concludes that there is, in that disease, a disturbance or dysfunction of motor units with a postural function. "This admission", he says, "could agree with the observation that the disease does not affect or only slightly affects muscles with considerable functional predominance of 'K' units". Sala (1958) reported the same findings in Motor neurone disease with comparable conclusions. My findings in Motor neurone disease, Myopathy and in various other neurological and non-neurological conditions do not confirm the loss of any particular modality of motor unit in any particular disease. The distribution of points on the MI/MD chart is entirely dependent on the condition of the muscle and the degree of tension developed in it. With progression of the disease and with deterioration of muscle

function, there was a distinctive and progressive shift of the NMUs in the MI/MD plot to the left of the reference line. No doubt this distribution (in advanced stages in the respective diseases) could lead to the conclusions of Sala and Bergamini if Tokizane's premise is accepted, but an alternative interpretation may be offered which does not require an arbitrary division of units by a line drawn through a scattergram. On clinico-pathological grounds alone objections may be raised to Bergamini's theory. The muscles of the face and the small muscles of the hand are capable of rapid contraction and have wide representation in area 4 of the motor cortex. According to Tokizane they should have a predominance of 'K'-units and be spared by muscular dystrophy. In the Facio-scapulo-humeral type of myopathy, the facial muscles may be among the first to be affected and may bear the brunt of the disease. The small muscles of the hand may be primarily and mainly affected in the rare type of Distal myopathy (of Gower).

Bergamini also tested the hypothesis that the phasic units (K-type) might be selectively lost in Parkinsonism and claimed to confirm this hypothesis. My findings agree in showing more MI/MD points to the right of the reference line and fewer to the left, but there is no evidence that this is due to a fall out of a 'K'-type. On the contrary, the whole plot is extended to the right by a higher incidence of very slowly firing units, and this change is confined to the affected side in unilateral rigidity (fig. 33). The same trend towards an increased incidence of units firing at abnormally slow rate (MI > 110

msec.) is seen in Friedreich's ataxia. It is an over-simplification and distortion of the facts to describe this as a persistence of 'T'-units with loss of 'K'-units.

In this context, Bergamini et al. (1961) reported observations on patients with hemiparkinsonism before and after stereotactic operation in the thalamic region. They noticed (in 3 patients) a postoperative "'shift' to the left" of the NMUs from the position they occupied previous to the operation. The points were shifted irregularly (i.e. not along any definite curve) to a zone which occupied a mid-position between the normal 'K' and 'T' curves of Tokizane. This supports my belief that Parkinsonian rigidity does not affect any particular group of NMUs or spare the other, but that the motor units discharge slowly in untreated Parkinsonism and their frequency of firing is capable of being increased postoperatively with consequent "shift to the left" of points on an MI/MD plot.

It seems as if we are back to the point we started. The functional organisation of human motor units was a dubious and controversial subject in the past and it remains much as it was at the end of the present series of experiments. It may be true that there is a functional specialization within the population of motor units in human muscle but this work does not support that the different types can be recognised by their firing characteristics assessed in Tokizane's way. The proposition seemed tenable that rhythmicity would break down as a motor unit slowed to a firing rate below its optimal working range and that the breakdown point might be slower for 'tonic'

than 'phasic' units, but there seems no primafacie reason why the degree of irregularity should then increase in a regular way. In fact no such regularity has been found in my experiments and no clear differentiation of unit types according to the slowest rate of rhythmical firing can be detected. Tokizanes own misgivings were indicated on page 33. My results point in the same direction, viz. that the difference between units represents a variation in the degree of servo control of firing frequency, but suggests a wide spectrum of response rather than two clearly defined types.

It is evident therefore, that a different interpretation is necessary to explain these findings. In Chapter 1 (B and C), there was discussed the possibility that the gamma system is used not only to improve the muscular performance during volitional movements but also, as an "ignition mechanism", to initiate movement and to maintain tonus. Granit and Holmgren (1955) suggest that voluntary contraction may be initiated by a gamma-efferent discharge which alters the 'bias' of the muscle spindles, and the 'misalignment' signal so generated activates the alpha motoneurones by the same pathway as the reflex activation (Chapter 1, B and C). This concept, not previously tested in the human subject, attributes an important role to proprioceptive feedback from muscle in the control of voluntary movement as well as the discharge frequency of the alpha motoneurones. A new series of experiments was therefore carried out by infiltration of procaine into the experimental muscle in order to study the activation of motor units deprived of gamma

innervation. The results and inferences of these experiments are discussed in the next Chapter.

CHAPTER 7

EFFECT OF PROCAINE ON THE VARIABILITY AND FREQUENCY OF FIRING OF SINGLE MOTOR UNITS

INTRODUCTION

In 1919, Liljestrand and Magnus demonstrated 'almost abolition' of rigidity of the triceps muscle of a decerebrate cat after injecting 0.5 to 1 ml. of 1% procaine into that muscle. With 4 to 8 ml. of procaine the last trace of tone and reflex response of muscle to nerve stimulation were removed but the response of the muscle to direct faradic stimulation remained intact.

Dilute alcohol (11-16%) was applied by Liddell and Olmsted (1929) to the medial popliteal nerve of a decerebrate cat. They reported 'rapid' disappearance of a stretch reflex, followed by a tendon jerk and then the crossed extension reflex, but the muscle tension produced by stimulating the nerve at 50/second did not disappear until later.

In the same year (1929), Gasser and Erlanger first showed by direct recording that "in general small fibres are blocked before the large ones" by cocaine but "the blocking is not affected with any precision". Their findings were confirmed on mammalian nerves by Heinbecker et al. (1934).

The same thing was found by Bremer and Titeca (1930) by intramuscular injection of procaine into the gastrocnemius-soleus muscle of decerebrate cats.

The effect on muscle reflexes of procaine and alcohol

applied in these ways appear to be identical. In the light of present knowledge, the findings of these workers appear to be due to the preferential paralysis, by procaine or alcohol, of the small motor nerve fibres to the intrafusal muscle fibres (the gamma fibres).

This view is supported by Leksell (1945) who recorded the compound action potential produced by stimulation of a ventral nerve root containing large and small motor fibres. He applied 1/500 ethocaine to the nerve central to the stimulating electrode and observed that "the effect upon the gamma wave was greater than the effect on the alpha wave".

On the other hand, Toman (1952) in reviewing the action of procaine stated that, "although a preferential attack on the small fibres is generally assumed, the rule is not universal". Matthews and Rushworth (1957) performed experiments on the cat to determine the relative sensitivity of the muscle nerve fibres to procaine, and concluded that the large fibres, whether afferent or efferent, are about equally sensitive, while the gamma fibres are much more rapidly paralysed. They found that five minutes after applying procaine to the nerve to soleus, the gamma wave disappeared, though the large motor and large afferent waves were unchanged.

There seems to be little doubt, therefore, that procaine first paralyses the gamma fibres. Since the gamma fibres supply exclusively the intrafusal muscle fibres (Leksell, 1945; Kuffler and Hunt, 1952; Granit and Kaada, 1953), this specific early effect of procaine was made use of in the next series of

experiments to study to effect of de-efferentation of the spindles in normal subjects as also in patients with muscular dystrophy (including Dystrophia myotonica) and Parkinson's disease (due to Paralysis agitans).

MUSCULAR DYSTROPHY

Despite many fruitful contributions, there are many deficiencies in our knowledge of skeletal muscles in terms of pathologic morphology, especially in relation to structural changes occurring in muscular dystrophy.

A final proof that the origin of this group of disorders is in the muscle fibres themselves is the demonstration of their intact nerve supply in the presence of severe histopathological changes in the muscles themselves. The conception that they all belong to a group of primary dystrophic diseases of muscle and also their cheif histopathological features were developed by the works of Erb (1891). Meryon (1864) was the first to establish that the spinal cord and the peripheral nerves remain healthy in this group of diseases while the muscles show granular degeneration. Griesinger (1865) was the first to make a surgical biopsy to confirm the presence of abundant adipose tissue in the affected muscles.

Duchenne in 1865 devised a trochar ("muscle harpoon") for biopsy of the hypertrophied muscles and with Charcot in 1871 confirmed the interstitial changes in the muscles and the absence of any change in the nervous system which he published in his monograph "L'Électrisation" (1872).

In 1876, Leyden drew attention to similarities between all familial muscular dystrophies, and 15 years later, in 1891, Erb described the chief histological features in all these diseases and drew attention to their similarity.

The condition of the spindles in Muscular dystrophies was also studied in the last century by Spiller (1897) and Grünbaum (1897) who found that "spindles remain unchanged in muscular dystrophy".

The condition of the affected muscles in the Muscular dystrophies is still being studied with interest in the present century by different workers in different parts of the world. Hereditary muscular dystrophy in the mouse has much in common morphologically with human muscular dystrophies. The differences that do exist are differences of degree rather than of kind (West and Murphy, 1960). The discovery of this disorder in mice has led to a renewed interest in the experimental approach to Muscular dystrophy.

The findings of contemporary workers support the observations made in the previous century. Michelson et al. (1955) did not observe any lesion in the central or peripheral nervous system in this group of diseases and concluded that Muscular dystrophy must be an inherent disease of muscle fibres themselves. Denny-Brown and Pearson (1953) noted that "the nerve plexuses do not show any degeneration, and the muscle spindles, free endings and autonomic nerve fibres remain intact" in Muscular dystrophy. Banker and Denny-Brown (1959) also noted that in dystrophic muscles of mice the muscle

spindles do not show any histological abnormality. The major histological changes in dystrophic mouse muscle are summarised by West and Murphy (1960) as "variability in the fibre size, relative and absolute increase in the endomysial connective tissue, coagulation necrosis of segments of muscle fibres, sub-sarcolemmic nuclear accumulations and internal nuclear rowing and regenerative activity".

While work on animal tissue in this disease is plentiful, that on human tissue is relatively scanty. Kirschbaum (1952) studied the human tissue in this group of disorders histologically. He found that there was no 'qualitative' histopathological difference in Progressive muscular and Myotonic dystrophies. The degenerative process in the muscle fibres frequently began in the outer part of a portion of a muscle fibre, and quickly advanced to the centre. The myofibrillary substance may withdraw from the periphery of the fibre to the centre. Some enlarged muscle nuclei tend to shift to the centre of the fibre. He also reported that the muscle spindles appeared normal even in severely degenerated muscle tissue. A few preserved nerve branches and portions of motor terminals were found inside disintegrating muscle fibres and this has also been reported by Falin and Kanarejkin (1941).

There is thus general support for the view that the muscle spindles are not affected in Muscular dystrophy. Sala (1915) is the only one (to my knowledge) who appears to differ from it. He claimed to have found in Pseudo-hypertrophic dystrophy that none of his material had a single entirely normal spindle,

although the intrafusal nerve was invariably normal in the early stages of the disease. He noticed also that when the atrophy of the muscles was intense, the nerve fibres in the spindle apparently suffered also, but the spiral and the plate like endings, which seemed always more resistant, were usually preserved even when the spindle was otherwise greatly altered.

PARALYSIS AGITANS

Idelsohn (1904) was the first to note the condition of the spindles in paralysis agitans. He studied the muscles of the hand and arm from autopsy material and noted that despite slight changes in the muscular tissue, the intramuscular nerves, the muscle bundle and the nerves to the spindle were unaltered. Camp (1907) studied the muscle tissue from eight cases of paralysis agitans (only one was a biopsy specimen from the forearm muscle) and found inconstant changes in the form of variable degrees of simple or degenerative atrophy, moderate fibrosis and proliferation of sarcolemma nuclei in the skeletal muscles. These observations were contradicted by Burzio (1902) and Redlich (1893-1894) who found the muscle fibres only slightly, if at all, affected.

It is scarcely conceivable that all the striated muscles have been examined for the presence of spindles, but it is stated that they appear in the 4th month of foetal life and are thereafter found in all the striated muscles with the exception of extra-ocular muscles, the diaphragm and the intrinsic muscles of the tongue (Byrnes, 1926). This study of the distribution of the spindles is interesting because it

is maintained that diaphragm, intrinsic muscles of tongue and the extraocular muscles are not affected in genuine paralysis agitans (Byrnes, 1926). Ordenstein (1867), however, described the involvement of extraocular muscles in the advanced stages of the disease.

In the early part of the present century the muscle tissue was repeatedly examined but the spindles were not made the object of special study until 1926 when Byrnes studied biopsy specimens from 14 patients suffering from paralysis agitans. He reported histological abnormalities of spindles which correlated with the degree of rigidity rather than with tremor or with duration of illness. He observed that the extrafusal musculature was unaltered, as a rule, and the intramuscular nerve trunks, except in the immediate vicinity of the spindle capsule, were of healthy appearance. In the spindles he described oedema of the periaxial and capsular spaces, degeneration of the intrafusal nerve fibres, vascular sclerosis, hyperplasia of the connective tissue elements and disintegration of the muscle bundle. The entire contents of spindle later underwent fatty changes, and were finally replaced by connective tissue scar. He never found any evidence of acute inflammatory reaction. The pacinian bodies and the 'neuro-tendinous end-organs' (Golgi end organs) showed normal histological appearance.

These reports, though they have not met with general acceptance suggest that differences in spindle function may be present between Muscular dystrophy and Parkinsonism. Any

difference of this type should be reflected in the voluntary contraction of muscle, as discussed in Chapter 1 (B and C) (and might explain the difference in the firing characteristics of the motor units in these two diseases as shown in Chapter 5); and further the gamma blocking effect of procaine should produce different results in each disorder. Experimental results to test this hypothesis are described in this Chapter.

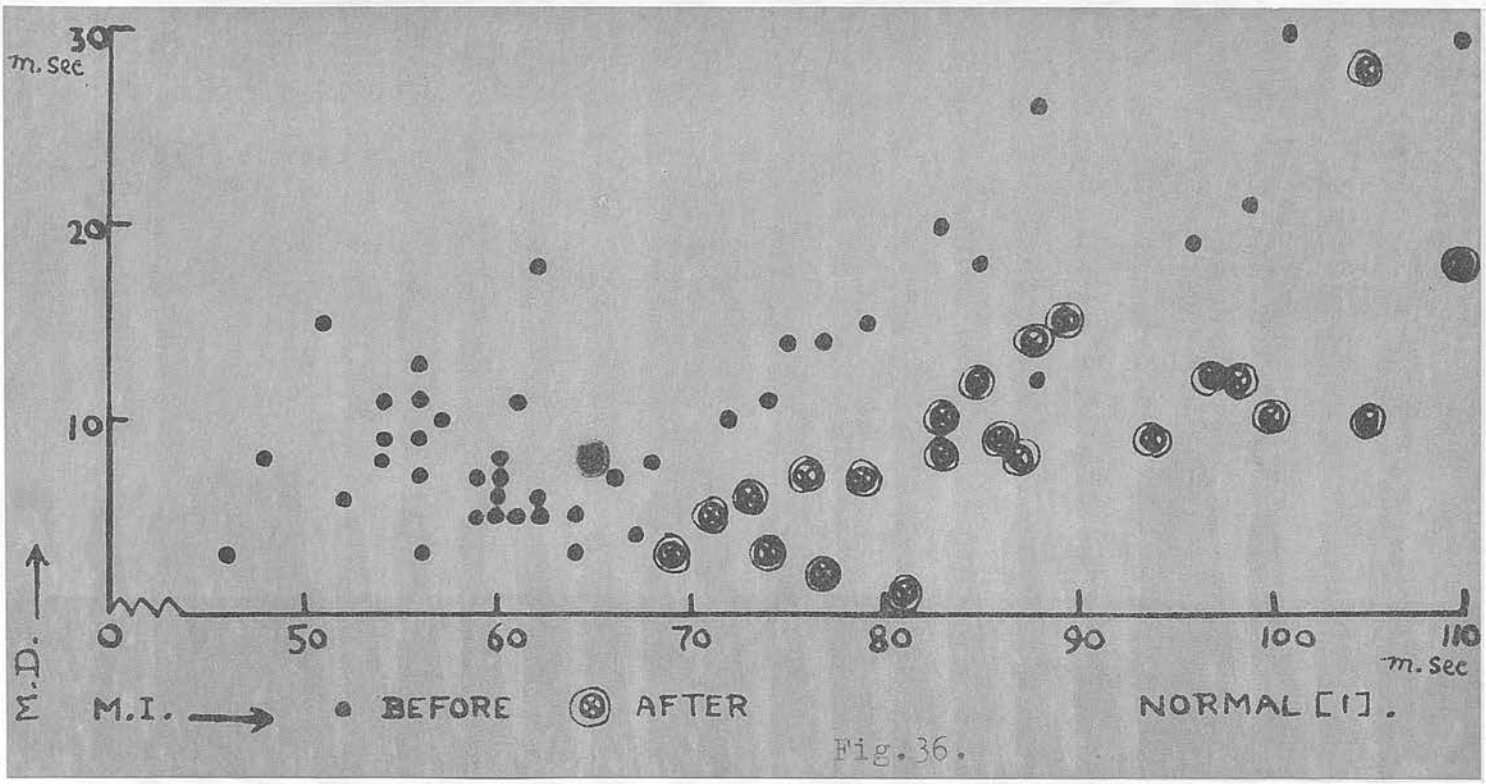
METHODS

The monopolar microelectrode, amplifier and the recording system used were the same as before.

The first dorsal interosseous muscle of the hand was investigated in all cases, not only because the load used for all these experiments could be kept at a standard level by using the frame (fig. 3), but because the spindles are said to be particularly abundant in the small muscles of hand and feet (Byrnes, 1926; Bowden, 1960).

All three loads used for experiments in Chapter 5 were also used in this series.

At the beginning of each experiment, a rhythmic discharge of single motor units was first identified on the oscilloscope screen. Their frequency of discharge was then noted and photographed at 3 different loads (giving a rest in between, if felt necessary, to prevent fatigue of the experimental muscle). Four ml. of 2% procaine hydrochloride was then infiltrated into the first dorsal interosseous muscle, keeping the microelectrode in its previous position so that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Σ.D.
M.I. ⟶
• BEFORE
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NORMAL [1].

Fig.36.

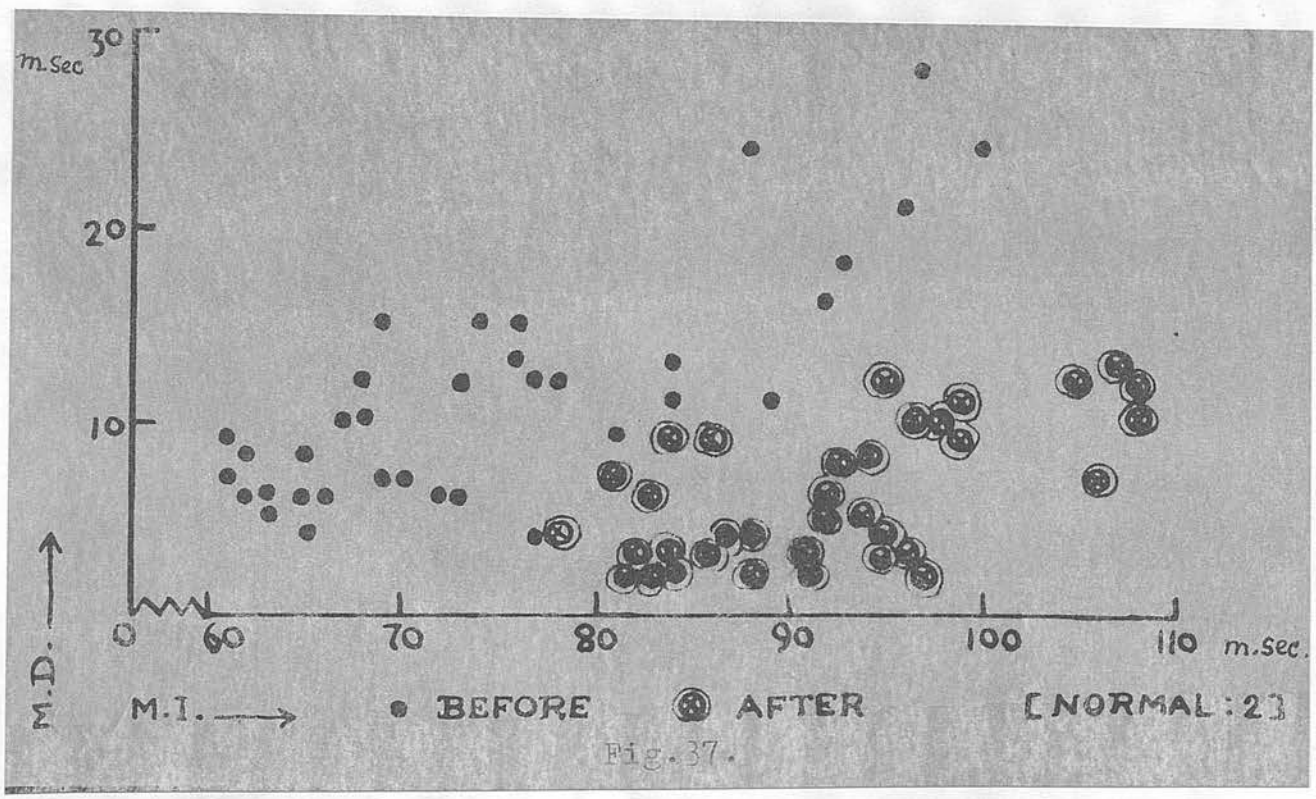
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Fig.37.

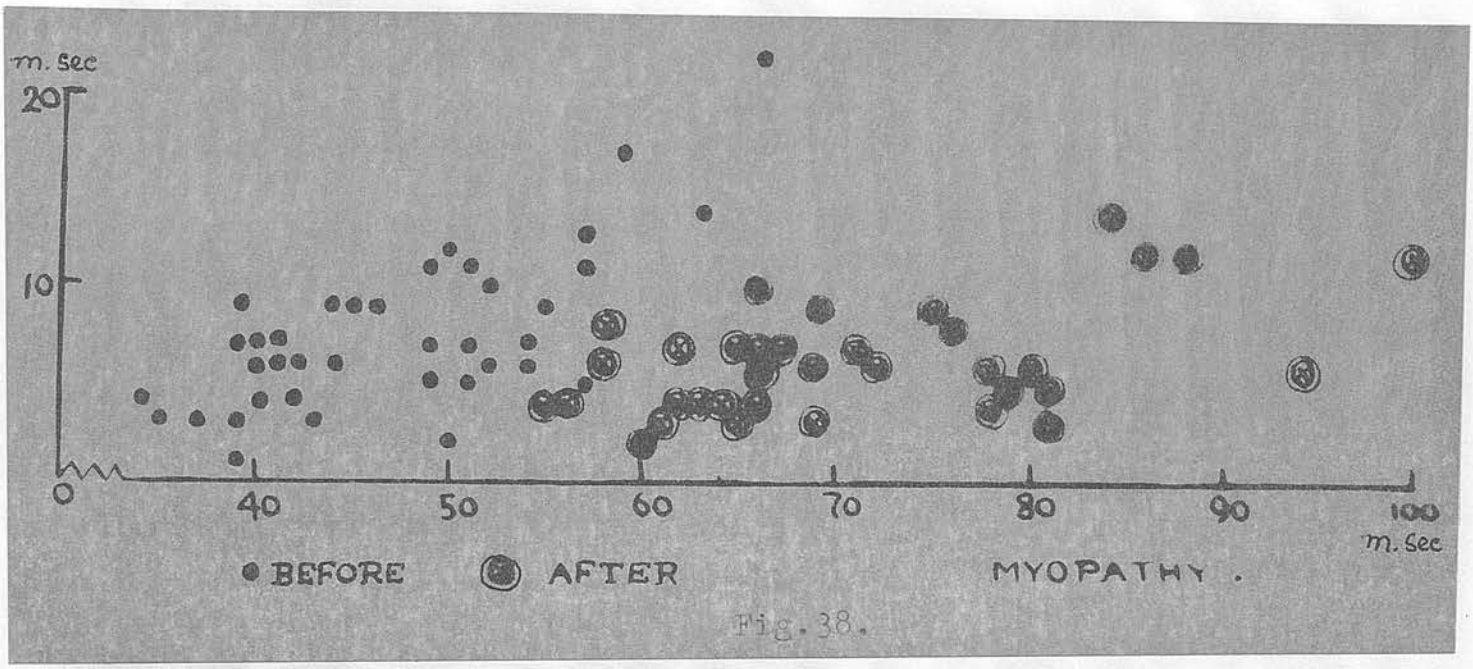
the behaviour of the same unit before and after infiltration could be examined. The second stage of the experiment was started 6 to 8 minutes after the infiltration of procaine (as Matthews and Rushworth, 1957, observed the paralysing effect of procaine on the gamma efferent nerves within 5 minutes). The patients were asked to relax in the interval between these two stages of the experiment. The same procedure as in the first stage was then repeated, after it was made sure that the same motor unit as in the first stage was still being recorded.

RESULTS

Observations were made on 10 normal subjects, 8 patients with Muscular dystrophy, 3 with Dystrophia myotonica and 15 patients with Parkinson's disease due to paralysis agitans.

As in Chapter 5, the mean interval (MI) and mean deviation (MD) were calculated to represent the frequency and the variability respectively of the motor unit discharges. As before, the MI and MD were the average of 4 to 8 spikes. The relation of MI to MD was charted as in Chapter 5.

Graphs from 2 normal subjects are shown in figs. 36 and 37 each chart representing samples of the firing pattern of a single unit before and after procaine infiltration. In fig. 36, only about 30% of the samples, before the injection, have MI exceeding 70 msec. and about 42% have MD more than 10 msec. After the injection, about 91% have MI more than 70 msec. and about 30% have MD more than 10 msec. The same trend is seen in the example charted in fig. 37. In this case, before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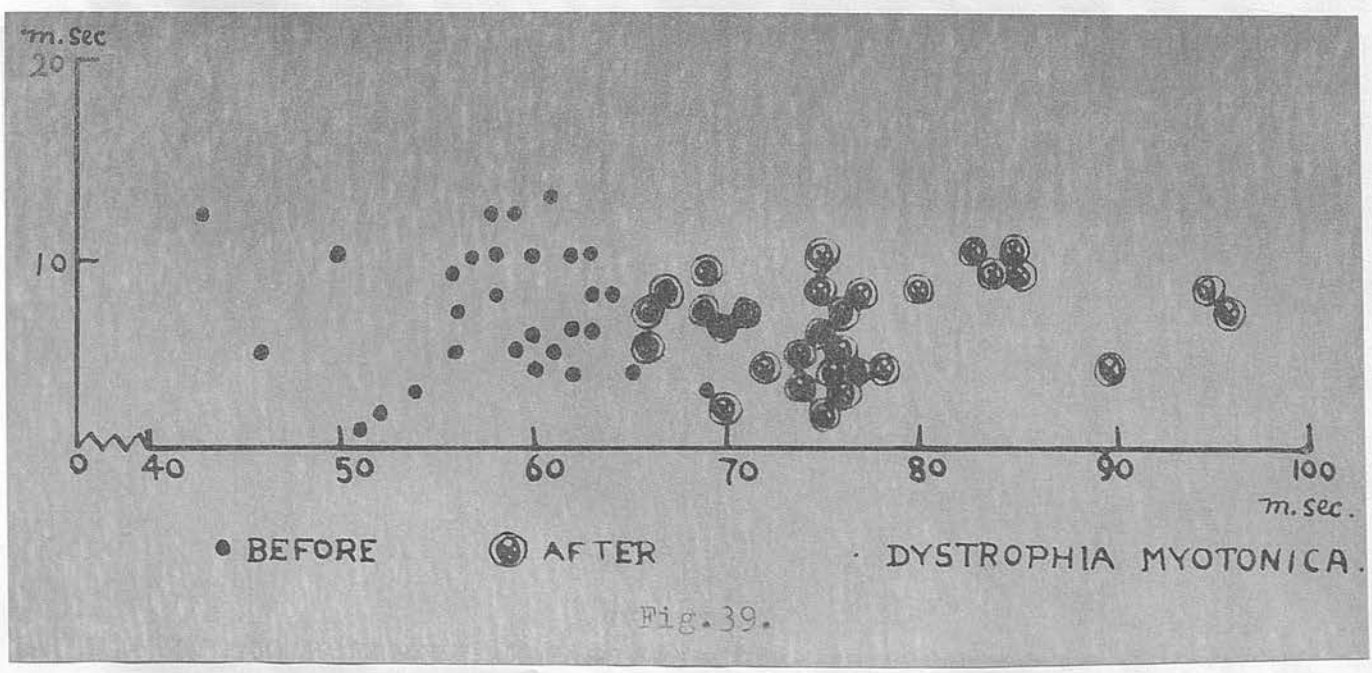
AFTER
MYOPATHY .

Fig. 38.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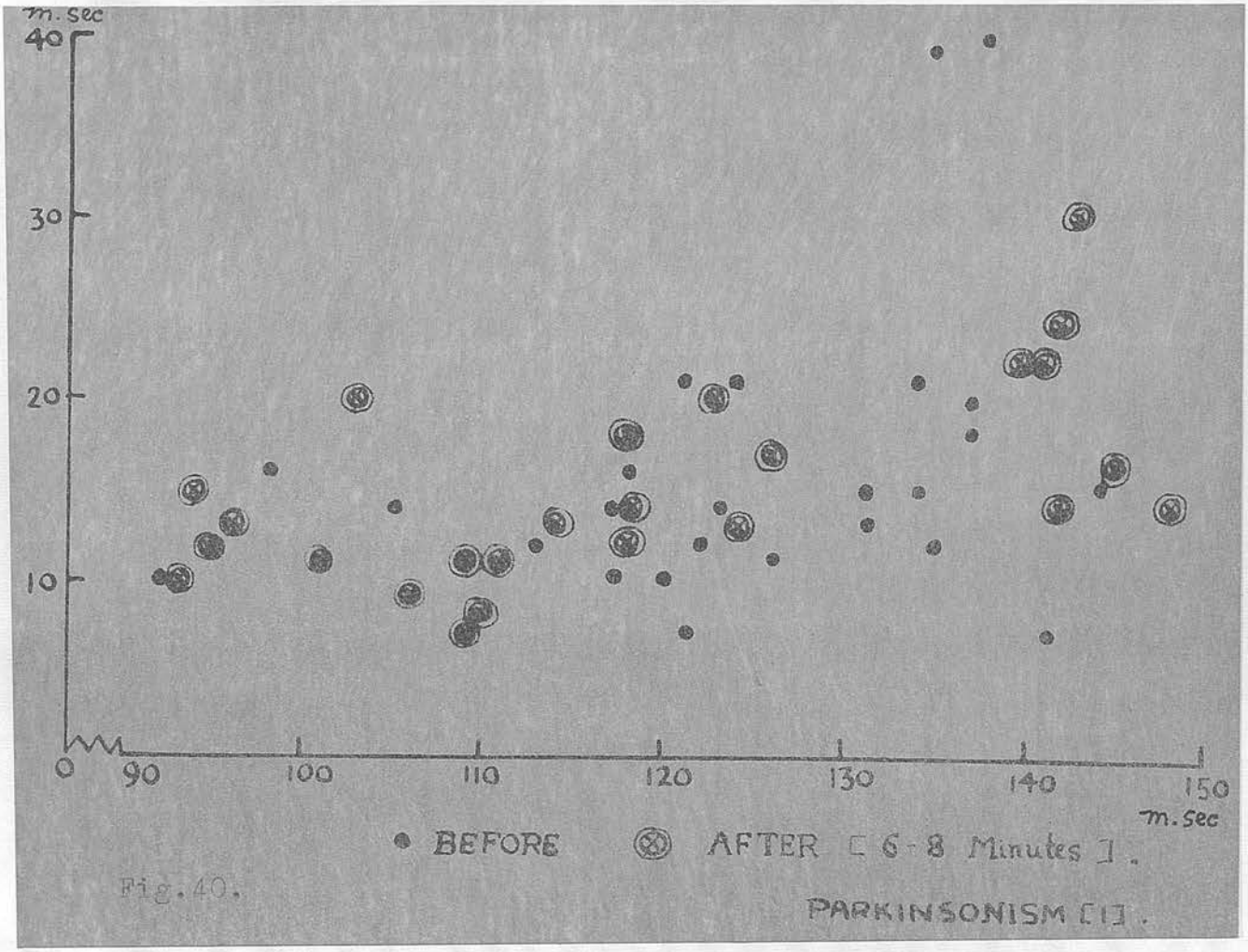
• BEFORE
AFTER
DYSTROPHIA MYOTONICA.

Fig. 39.

procaine, about 29% of the points plotted have MI more than 70 msec. and about 50% of them have MD more than 10 msec., while after the injection, about 97% have MI more than 70 msec. and about 14% have MD more than 10 msec. In both cases the muscles sustained standard loads with slower and more regular discharge rate of the motor unit after the injection of procaine into the muscle.

Procaine was injected into the muscles of 8 patients with Muscular dystrophy. The example in fig. 38 is typical of all. In this particular example, only about 5% of the firing patterns have MI more than 60 msec., and about 20% have MD more than 10 msec. before procaine is injected. After procainisation, about 90% have MI more than 60 msec. and about 10% have MD more than 10 msec. Dystrophic muscle thus responds normally to injection of procaine, the firing frequency of single motor units becoming slow and variability decreasing after the infiltration of procaine. The variability of the firing frequency of the motor units is usually greater at slow rates of firing, but after procaine the regularity is maintained even at slow rates.

Three patients suffering from Dystrophia myotonica were examined next. A representative example is shown in fig. 39. As the peripheral muscles were also affected in the disease process with moderate degree of wasting, the firing rate (for standard loads) was faster than in the previous examples (see Chapter 5). About 3% of the sample had MI more than 65 msec., and none exceeded 70 msec. before procaine. About 12% of them had MD exceeding 10 msec. After the procaine injection,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m. Sec
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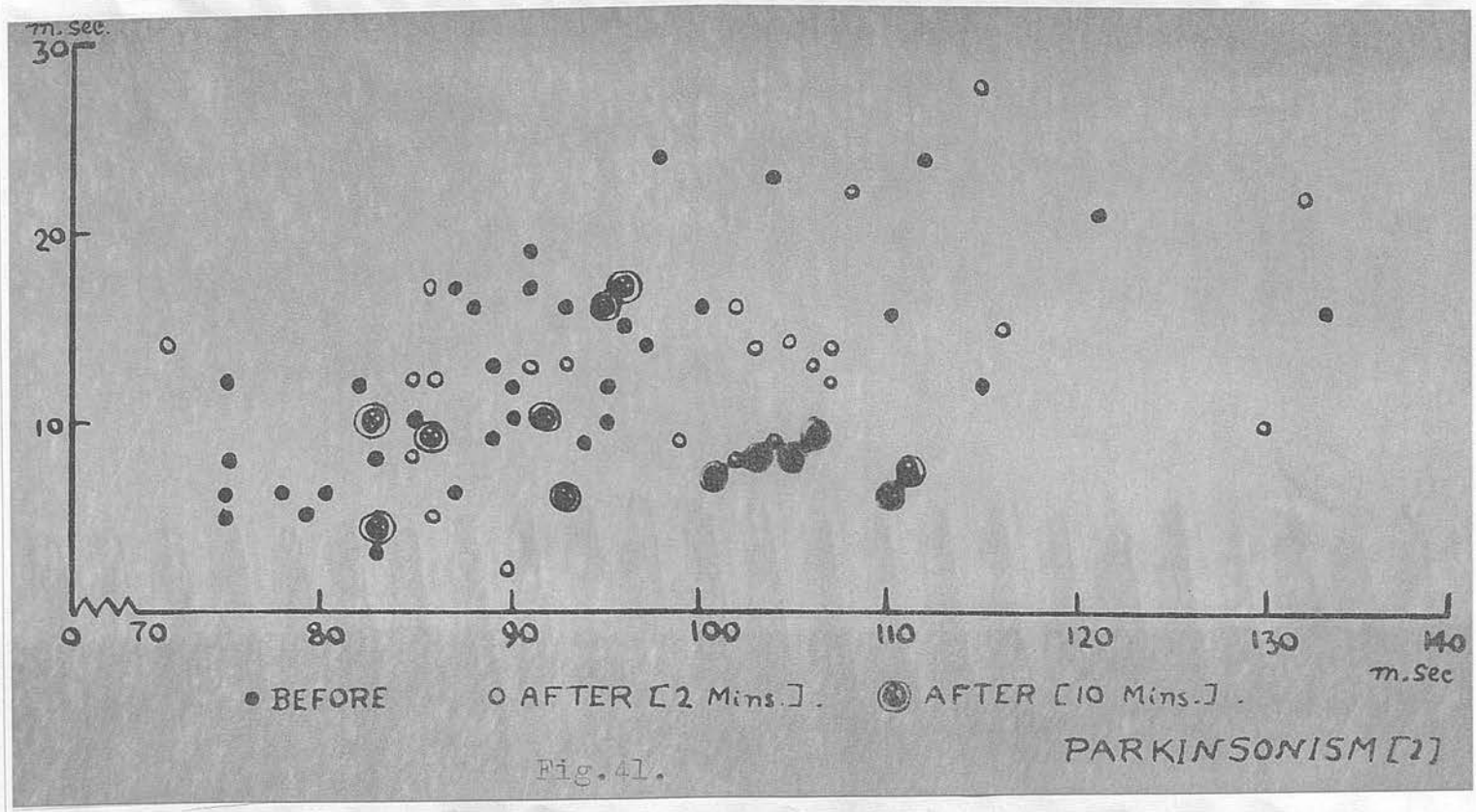
⊗ AFTER [6-8 Minutes].
PARKINSONISM [1].

Fig.40.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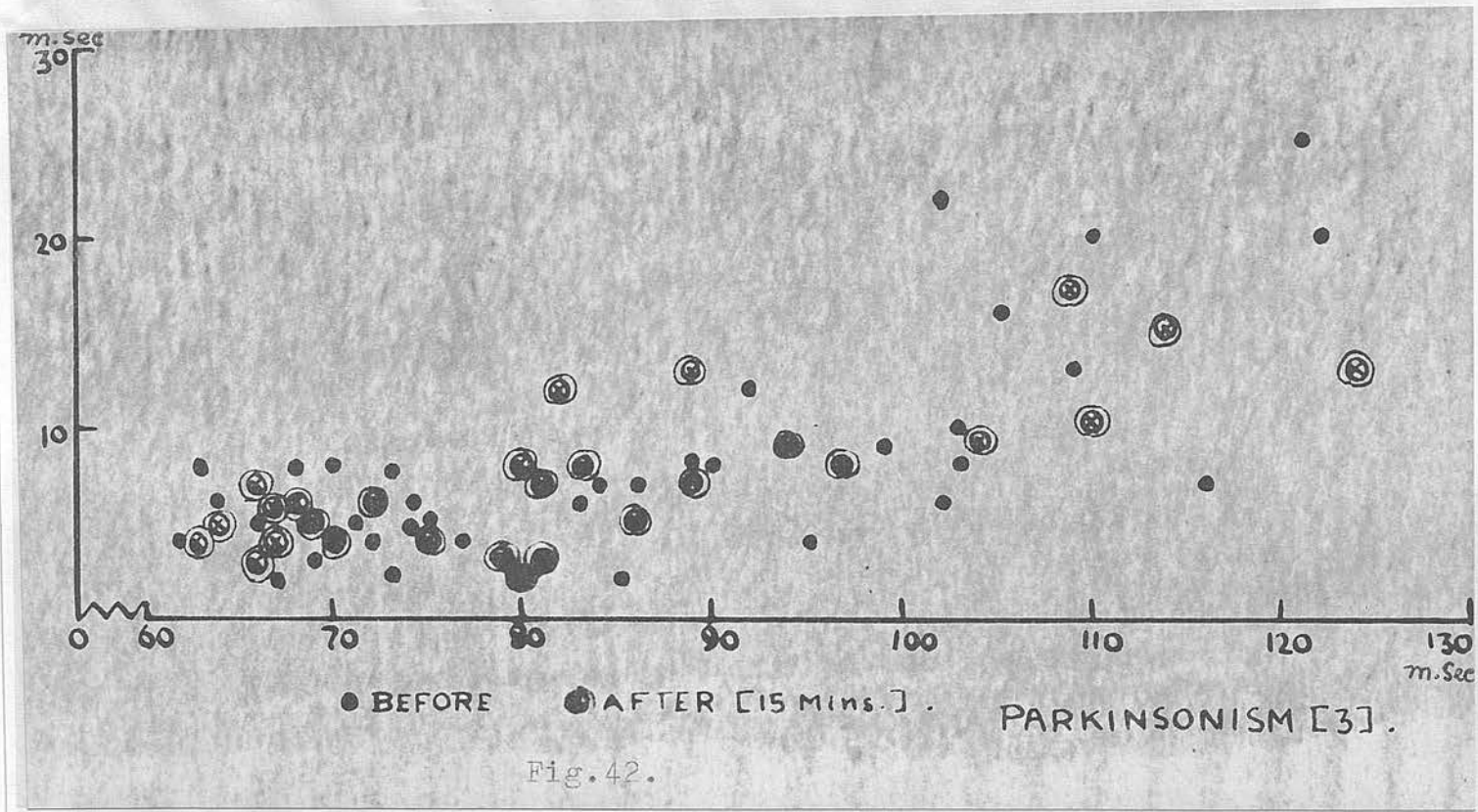
o AFTER [2 Mins.].
⊗ AFTER [10 Mins.].
PARKINSONISM [2]

Fig.41.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● BEFORE
● AFTER [15 Mins.].
PARKINSONISM [3].

Fig.42.

every sample recorded had a MI greater than 65 msec. and about 77% exceeded 70 msec., while none had a MD more than 10 msec. even at these very slow rates of firing. This response is the same as in normal subjects and in cases of Muscular dystrophy of non-myotonic type.

Fifteen patients suffering from well established Parkinson's disease (due to Paralysis agitans) with marked rigidity were examined. Fig. 40 represents the response of a female patient of 60 years. Here, as in previous experiments, 4 ml. of procaine was injected and records were made 6 to 8 minutes after the injection. The figure shows that the distribution of the MI/MD points on the plot is unchanged by the injection of procaine. It was demonstrated in Chapter 5 that the firing rate of motor units in Parkinsonism is much slower even in the absence of procaine. It now appears that procaine does not increase this difference from normal; but the recording conditions were altered in some cases to make sure there was no transient or delayed effect.

Fig. 41 shows representative results from a man of 55 years. It shows the same motor unit at 3 different times, before, at 2 minutes and at 10 minutes after procaine injection. There is no indication of an early or late response to procaine - the scatter of points being the same at each time.

Fig. 42 shows the firing pattern from another patient of the same group, before and 15 minutes after procaine. Again, no change could be detected.

It will be seen that the firing pattern of motor units in

paralysis agitans resembles that of normal subject and the patients with Muscular dystrophy after infiltration of procaine and that such infiltration causes no further change in paralysis agitans.

DISCUSSION

Eldred, Granit and Merton (1953b) made a selective de-efferentation of the gamma fibres in the decerebrate cat and observed that this led to a sudden drop of spindle frequency. At the same time, "the discharge became regularized and, at all initial tensions, stabilized frequently below the value of the spindle in possession of its gamma efferents". This particular experiment was carried out over a large range of tension from zero upwards. "Even at zero tension, the activated spindle (of an intact animal) had a higher frequency than the de-efferented spindle".

'Acute' de-efferentation of the gamma fibres would therefore be expected to lead to slow and regular discharge from the spindles, which in turn would slow down and regularize the alpha motoneurone activity (if the tension and other experimental conditions are kept constant before and after the operation).

Infiltration of procaine into the muscle should lead to this result if it truly blocks gamma motor fibres selectively (Matthes and Rushworth, 1957). The slow, more regular discharge of motor units reported above after procaine infiltration in healthy subjects is strongly suggestive of a

'drop of spindle frequency and its regularization' as a result of their 'acute' de-efferentation. This result is predictable from the 'servo' theory of voluntary muscular control, but would not otherwise be expected.

The patients with muscle weakness due to Muscular dystrophy and Dystrophia myotonica responded to procaine in the same way as the normal subjects. This is indirect confirmation that the normality of spindles reported in these conditions by the histologists (mentioned in the introduction) extends to their function in voluntary contraction of muscle.

The results of the present series of experiments on rigid muscle suggest that procaine infiltration does not in any way alter the frequency and the variability of firing of the motor units. The result can only be interpreted as due to pre-existing interruption of the gamma efferents due to the disease process which could not be further affected by procaine. In other words, for some reason or other the muscle spindles in patients with Parkinsonism have lost active innervation and hence lost their controlling influence on the alpha moto-neurones. The "degeneration of the intrafusal nerve fibres" and "disintegration with ultimate replacement of the spindles by connective tissue scar" which were observed in Parkinsonism by Byrnes (1926) may be genuine, possibly as late sequelae of cessation of central muscle spindle innervation after years of inactivity. It should certainly be reinvestigated by modern methods.

The demonstration of disappearance of rigidity by

intramuscular injection of novocain into the biceps brachii muscle by Walshe (1924) is in apparent conflict with the present findings. He used 18-25 c.c. of novocain and noticed the maximum effect from 15 to 25 minutes after the injection. This dose of novocain in the observed time could block the large afferents (which Walshe himself had suggested) or the efferent alpha motoneurones (Matthews and Rushworth, 1957) and the reported abolition of rigidity might be due to either or both of these factors.

The findings of the present series of experiments along with those described in Chapter 5 are discussed in more detail in Chapter 9 but first an unexpected observation in Parkinsonism must be reported.

CHAPTER 8

PAIRED RESPONSE IN PARKINSONISM

INTRODUCTION

James Parkinson (1817) believed that the whole complex of Parkinsonism including tremor was due to abnormal function in the upper part of the spinal cord and the medulla oblongata. Though a great deal of clinical, pathological and experimental work including surgical operation for the Parkinsonian syndrome have led us to believe that the site of pathology is much higher, in the basal ganglia, it is interesting to note how progressively we are retreating down the neuraxis. We now realise that the part played by the spinal cord and its connections (see Chapters 7 and 9) is not insignificant, and so an important pathological mechanism of Parkinsonism lies much close anatomically to what Parkinson suggested over a century ago.

The importance of this local pathology is once again realised when an accidental observation was made which is the subject of this Chapter.

OBSERVATION

Methods and experimental procedures are the same as before.

Observations were made on 10 patients with Parkinsonism due to paralysis agitans. All of them had tremor as a symptom in addition to rigidity but records were taken when there was no overt tremor or when tremor was so slight as not

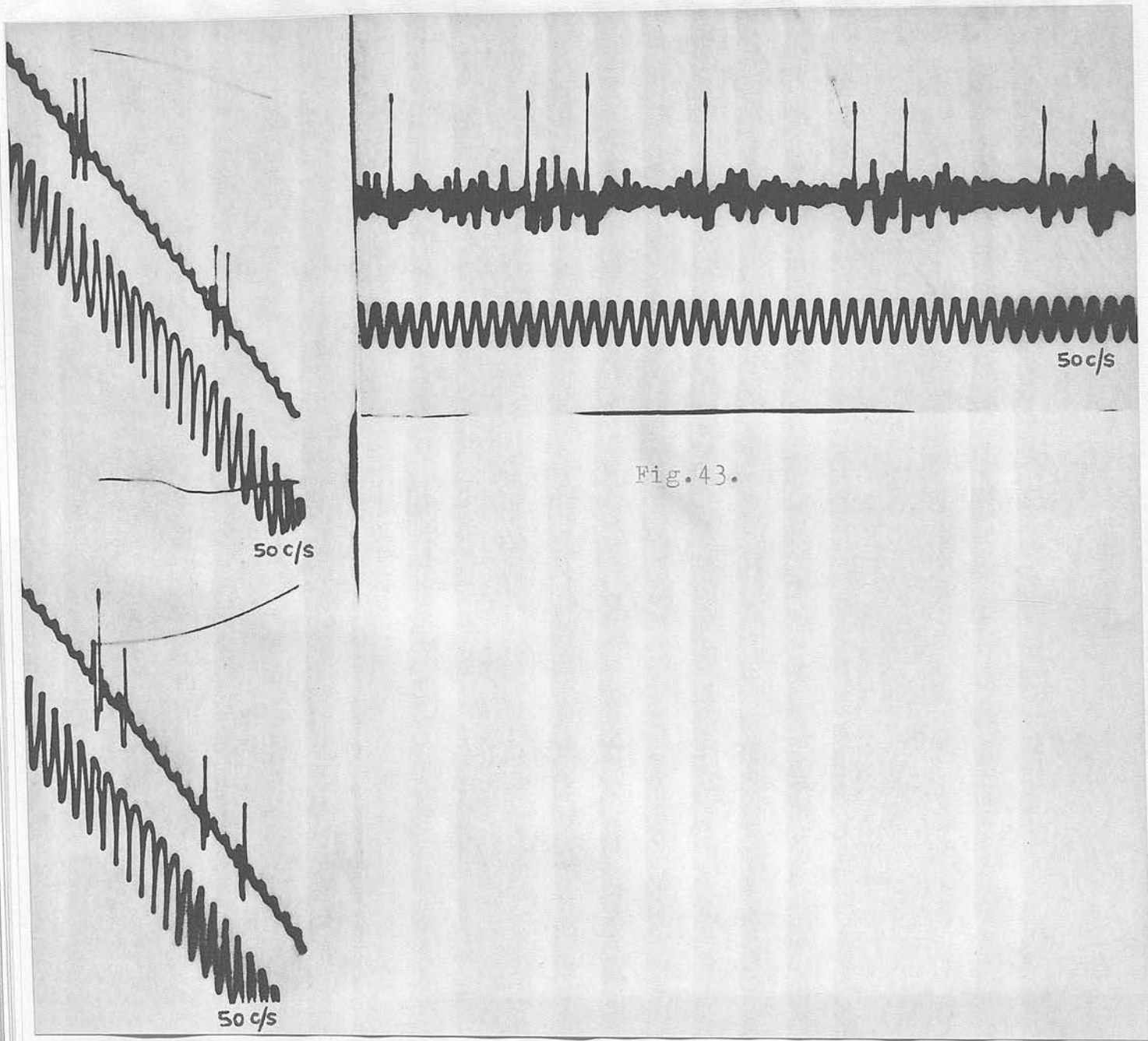

Fig. 43.

to affect the picture.

A prominent feature of the firing pattern of single motor units during sustained voluntary contraction was a tendency for the spike discharge to be grouped in pairs (fig. 43). The intervals between the two spikes were extremely variable, from 20 msec. to over 80 msec. but usually between 30 and 60 msec. When there was overt tremor during any experiment, it was repeatedly observed that not only was there synchronous discharge of a number of different motor units corresponding with each twitch of a tremor, but individual motor units also discharged twice in succession resulting in a paired response. In other words, paired response of a single unit was found along with synchronous discharge of multiple motor units when tremor was overt, but when it was not so, the occurrence of paired response was found to be unpredictable and it was then seen to be irregularly distributed throughout a particular record without showing any temporal predilection.

DISCUSSION

If we adhere to the definition of a motor unit by Adrian and Bronk (1929), Denny-Brown (1929) and others that "a record may be assumed to arise from single units when all the action potentials are approximately of the same shape and when they form part of a regular rhythmic series", there is little doubt that the second component of the paired response arises from the same unit as the first one. There may be slight dissimilarity in the spike heights at times, but "similar or

greater dissimilarity is often seen during repetitive discharge of the same unit during sustained effort" (Gilson and Mills, 1941).

It had been observed by many workers (Adrian and Bronk, 1929; Denny-Brown, 1929; Eccles and Hoff, 1932; Hoff and Grant, 1944) that during firing of a single motor unit, it is not uncommon for the motor neurone to give one or two "double discharges" specially when the neurone is firing at very near its threshold. HoffandGrant (1944) put forward a rigid definition that a paired spike can be called a "double discharge" only when the second beat arises from the same unit as the first one and when the interval between them lies between 2.9 and 20 msec. The second spike may be somewhat smaller in amplitude and of greater duration than the first (Gordon and Holbourn, 1949). These "double discharges" are most commonly seen at the beginning of any contraction, less often at the end (Gilson and Mills, 1941), and this fact led Gordon and Holbourn (1949) to believe that double discharge allows a large initial development of tension which could then be maintained by a fairly low frequency of firing. Kugelberg (1948) observed that "double discharge" may possibly be somehwat more frequent in anterior horn cell diseases. He believed that the site of production of these "double discharges" must be somehwere in the periphery since they can be "faithfully reproduced" by peripheral electrical stimulation. Denslow (1948) found that a long pause always followed a "double discharge" and considered that this was a striking feature.

The paired responses found in Parkinsonism and reported here for the first time, are different from the "double discharges" observed by these workers. The minimum interval between these spikes is always bigger than the maximum observed between the two components of a "double discharge". They are not specially frequent at the beginning but in fact, are distributed irregularly throughout an isometric contraction. They are never seen in Motor neurone disease which is one of the conditions (e.g. anterior horn cell disease) where Kugelberg (1948) observed the "double discharge" to be particularly common. No unusually long pause has ever been noticed to follow a paired response regularly. Therefore, it seems clear that these paired spikes cannot be called "double discharges" as defined above. They will be provisionally called "paired responses".

In general, the rhythmic pattern of paired response resembles strikingly the ECG appearance of pulsus bigeminus where two beats occur in quick succession followed by a long refractory period. The extraystole which forms the second component of this coupled beat arises spontaneously as a result of the presence of a "supernormal phase" in the recovery cycle following the first beat. In a variety of tissues, e.g. axons, sympathetic ganglia, myoneural junction, etc. a single subliminal stimulus may lower a threshold so much that a second stimulus, itself normally subliminal, may after producing a "temporal summation" with the preceding one reach a threshold intensity and thus produce an impulse (Hoff and Grant, 1944).

The paired response in Parkinsonism might at first sight suggest the presence of a supernormal phase following an original motoneurone discharge which can sometimes be raised above firing threshold in the presence of constant bombardment by afferent impulses, which thus acts as a "detonator" stimulus for the second discharge of the paired response. This theory is untenable because of the time factors involved. A supernormal phase following a motoneurone discharge varies from 3.0 to 15.0 msec. (Hoff and Grant, 1944). This interval is too short to explain the observed latency of 30 to 60 msec. between the two components of a paired response. Moreover, the duration of the recovery period following the second discharge of a pair is also significant. The subnormal period following repetitive firing of an excitable tissue tends to summate and this is the reason why there is always a long refractory period after pulsus bigeminus. It probably also explains the long period of electrical silence after a "double discharge" described by Denslow (1948) where the pair were grouped within the time necessary to consider supernormality and summed subnormality in explanation. No "compensatory pause" has ever been noted to follow a paired response in this work though I have been alert to the possibility of its occurrence. The wide gap between the discharges forming the pair and the absence of a "compensatory pause" make it most unlikely that the paired response is due to an abnormal excitability cycle of the motoneurone.

The question of whether Parkinsonian tremor is a spontaneous rhythm of central origin or a chain of reflex events is not merely of great theoretical interest as its proper solution would have repercussions on both surgical and medical treatment. Jung (1941) has pointed out that the rhythmic trains of impulses of tremor cannot originate in the brain itself, and Schwab andCobb (1939) failed to find any correlation between cortical electrical activity and the Parkinson tremor rate. Jung (1941) favoured the opinion that the internuncial neurones of the spinal cord should be held responsible for it. This is reminiscent of Forbes's (1929) "reverberating circuits", i.e. circuits of excitation which persist for considerable periods. Forbes (1929) and Lorente de Nó (1939) assumed the existence of such circuits and Delisle Burns actually suggested that the internuncial neurones are the site of origin of the rhythmical discharges. But the experiments of Luschnat (1954) on monosynaptic reflexes in the human subject and that of Lippold et al. (1958) on rhythmic stretching of muscle in a decerebrate animal rule out a central rhythm. In fact, though Delisle Burns (1958) supported the theory of "reverberating circuits", he emphasized the dependence of excitation circulating in this circuit on external impulses. Any chain of interconnected neurones, such as the internuncial system of the cord is potentially capable of simple oscillation if it is excited and maintained by impulses from outside the system.

It is well known that tremor in Parkinsonism appears after

a period of quiescence and it then tends to build up progressively as if each tremor contraction is reinforcing the succeeding one. Conversely, patients are often able to reduce or abolish the tremor altogether by immobilizing the affected limb or by active voluntary contraction of it. Therefore, it seems that whatever may be the initiating cause, the stretch reflex impulses set off by each tremor burst help to maintain it (Bishop et al., 1948-49). The importance of the afferent inflow is further suggested by the effect on tremor of extensive posterior root section of a rigid limb, as was done by Pollock and Davies (1930) who observed that "although the tremor was not abolished, it was changed in amplitude, rhythm and rate".

It can be argued that the motoneurone pool would have a tendency to fire synchronously if some excitatory or inhibitory system spreads rhythmically along the supposed "reverberating circuit" (Lippold et al., 1957). Hufschmidt (1959) suggested that the inhibitory influence from the Golgi tendon organs is very much increased in Parkinsonism (see Chapter 9). According to him, spinal motoneurones in this condition must be over reacting to these inhibitory impulses which might spread rhythmically along that circuit. "The tremor", he said, "thus originates as a chain of heightened inhibition reflexes, and hence an additional heightening of tension or decrease of tension ..... can predictably influence the tremor according to its point of application to the tremor cycle".

This argument may very well explain the synchronous discharge of mutliple motor units, but it is difficult to

comprehend how it can give rise to a paired response of the same unit. This must be the manifestation of repetitive discharge of the same motoneurone, due to some local cause (which has not been proved) or successive facilitatory stimuli must reach the motoneurone from some source, spinal or supra-spinal.

A long maintained excitatory state would lead to repetitive firing of motoneurones with a repetition period determined mainly by Renshaw inhibition. The period of 30-60 msec. between spikes of a paired response would be compatible with this (see Chapter 3). The crux of the problem remains the source of the maintained excitatory state affecting the motoneurones. According to contemporary thinking this implies sustained activity of spinal interneurones. Conventional views on Parkinsonism would attribute this to tonic excitation from brain stem facilitatory centres. The observations reported in Chapter 5 and discussed in Chapter 9 suggest the presence of some supraspinal inhibitory centre or tonic inhibition of peripheral origin (Hufschmidt, 1959). Neither mechanism is mutually exclusive, and indeed both may be necessary to resolve a 'paradox' which this work has shown. (See also Chapter 9).

CHAPTER 9

INTERPRETATION OF THE OBSERVATIONS REPORTED IN CHAPTERS 5, 7 and 8

The work reported in this thesis was designed to investigate Tokizane's claim to differentiate phasic and tonic motor units in human muscle. The claims were not confirmed but some new observations have been made (reported in Chapters 5, 7 and 8) and these require further discussion.

1. WEAK MUSCLES

In some neurological and non-neurological conditions associated with muscle wasting, I have noticed that the frequency of firing of motor units has increased considerably compared to a normal muscle with same or lesser load. The increase in frequency varies directly with the degree of wasting of the muscles concerned irrespective of its aetiology. Weddell et al. (1944) have previously observed that "paretic muscles usually have higher frequencies than normal muscles". This must necessarily be so if one recollects (see Chapter 1, D, d) that there are two mechanisms by which power of muscular contraction is increased: (a) by recruitment of more units, or (b) by increased firing rate of units. If there is a dearth of units (e.g. in neurogenic atrophy) or the units are fully recruited but mechanically inefficient as in Myopathy (Lenman, 1959) and presumably in periarthritic wasting, only the second mechanism is possible. Thus a "shift to the left"

in the MI/MD curve may be simply an indication that all recruitable units are used at the faster (and so most rhythmic) part of their firing ranges.

It is also possible that there is some adjustment at the level of spinal interneurones. Efferent motoneurones probably discharge at rates determined by facilitation and inhibition transmitted by spinal interneurones (see Chapters 1, B and C) where integration occurs between the stimulatory impulses from the muscle spindles and the inhibitory ones from the tension receptors (Hufschmidt, in press). In other words, the frequency of firing of motor units will be increased when a normal firing rate does not suffice to reduce the length difference recorded by the spindles, or when there is less feedback from the tension receptors, the former condition applying in the loaded paretic muscle, the latter when it is unloaded.

Sandow and Brust (1958) studied 'tetanus tension' of dystrophic mouse muscle because it measures the maximum force which can be developed by a muscle. They found that "on a unit weight basis dystrophic muscle produces only 0.64 times the tetanus tension of the normal", and they remarked that the "rate of development of tension" in dystrophic muscle, in comparison with normal, "is greatly reduced". This is due to the smaller mass of contractile tissue in dystrophic muscle. Contractile tissue is decreased in all wasted muscle and so it may well be that the tension produced in these wasted muscles is also always less than normal healthy muscle. It follows from this that the total tension developed is less than would

normally be the case for a particular rate of firing of a unit in that muscle. Each unit will thus be less inhibited by the tension receptors with consequent increase in its firing rate.

2. FRIEDREICH'S ATAXIA

The nature of areflexia in Friedreich's ataxia was studied in detail by my colleague, R. Levy (1961) of this unit. He reported that the 'H' wave of Magladery, evoked in calf muscles by electrical stimulation of the sensory fibres of the medial popliteal nerve, is easily obtainable in patients with Friedrich's ataxia in whom ankle jerks are absent. This finding suggests that the monsynaptic reflex arc is intact in these patients proximal to the stretch receptors, and he concluded that, "although end organ insensitivity remains possible, the spindle depression may result from the absence of supraspinal facilitation". It is usually considered that supraspinal facilitatory and inhibitory influences are brought to bear on the motoneurones of the spinal cord either directly (the "synaptic pool" of Sherrington) (see Chapter 1, A) or via internuncial neurones (Suda, Koizumi and Brooks, 1958). The servo theory of Granit and colleagues (see Chapter 1, B and C) implies that supraspinal influences can also affect anterior horn cells (alpha motoneurone) excitability indirectly by their actions on the muscle spindle mediated by the gamma efferent system. If Levy's (1961) findings are confirmed it would appear that there is loss of supraspinal facilitation in Friedreich's ataxia and furthermore that some of this loss is

due to failure of normal proprioceptive feedback drive from the "servo-loop". The unfacilitated spindle is a less efficient measuring instrument of the length difference between intra and extrafusal muscle fibres and one would predict diminished alpha-neurone driving during voluntary movement. This is exactly what is found in Friedreich's ataxia. The normal findings in tabes dorsalis conflict with this idea but it may well be that afferent fibres from the inhibitory receptors, such as Golgi tendon organs are also affected in tabes whereas the afferent fibres are normal in Friedreich's ataxia so that only facilitation is lost and peripheral inhibition becomes dominant.

3. PARKINSONIAN RIGIDITY

Very little is known about the pathophysiology of rigidity. Any new information about it raises almost as many questions as it answers. Apart from the clinical correlation with disorders of the basal ganglia, little is known about the central disturbance of innervation leading to rigidity. The Sherringtonian concept (see Chapter 1, a) that the lower motor neurone is tonically activated by some discharges "released" (in Hughlings-Jackson's sense) from the basal ganglia, as the lower motor neurone is a "final common pathway", requires re-examination in view of the suggestion that alpha motonuerone activity follows spindle discharges initiated by gamma motoneurones which are bombarded by extrapyramidal impulses (see Chapter 1, B and C).

The degree of tonic innervation of spindles of limb muscles can be actively increased clinically by Jendrassik's

manipulation. The latter is absent in a purely rigid muscle (Hassler, 1955 and 1956-57). "Thus the capacity to innervate the muscle spindles actively disappears" and so, with this "the servo mechanism of length loses its adaptibility" in Parkinsonism (Hassler, 1955). This loss may well account for the innervation difficulties in these patients. They lose, as is well known, all automatic associated movements which depend to a considerable degree on the regulating mechanism of the muscle spindles. It is just in the proximal muscles that the muscle spindle mechanism automatically acts against gravity (Hassler, 1956-57).

Further supportive evidence for deficiency of central gamma innervation is the occurrence of Parkinsonism after administration of chlorpromazine (Sommer, 1940; Hoffmann, 1951). This is in keeping with the observation by Henatsch and Ingvar (1956) that spindle activity in the animal is inhibited promptly after intravenous administration of chlorpromazine, probably by inhibition of supraspinal facilitation of gamma motoneurones.

Hufschmidt and Schaltenbrand (1959) suggested that, "with regard to normal proprioception", as also in some pathological conditions, "the polysynaptic reflex arc and the autogenous inhibition (from the Golgi tendon receptors) play much more important role than do the proprio reflexes" (i.e. the monosynaptic reflex). Hassler (1955) also observed that the myotatic reflexes of Liddell and Sherrington (or Dehnungs reflex of Foerster) responding to slowly occurring stretches and

relayed through internuncial neurones are enhanced in Parkinsonism. They are conducted (see Chapter 1, B) by thinner afferent fibres arising from the flower spray endings (secondary endings). Asai et al (1958) went a step further and suggested that in rigid muscle "the polysynaptic facilitating influences originating in the muscle spindles maintain the whole voluntary innervation".

The findings of these workers suggest that even with complete interruption of efferent gamma fibres (and consequent breaking of monosynaptic reflex arc), it is possible to have a wide range of co-ordinated voluntary movements such as are retained by patients with Parkinson's disease. The result of experiments on rigid muscle reported in Chapter 7 is in keeping with this view.

The slow firing rates of the motor units during voluntary contraction in patients with Parkinson's rigidity is still more surprising. As has just been said, the increased muscle tone of this disorder since the days of Hughlings Jackson, has been considered to be a manifestation of "release" of facilitatory impulses from the basal ganglia. One would have expected to find that units fired at a frequency in the upper range of normal. If the servo-theory is valid and the role of the spindle loop is paramount, this concept obviously requires revision.

If the rigid muscle has lost its capacity to adjust its length by means of the automatic regulating cycle from the (gamma-biassed) nuclear bag ending of the spindles (as has just

been suggested), the other servo mechanism of muscle tension may control the muscular contraction. Thus Hufschmidt (1959) found that inhibitory impulses from the tension receptors, e.g. Golgi organs, are greatly increased in this disease to such an extent that the slightest additional muscle tension is followed by inhibition. From the mechanical point of view this means, "more tension is reported from the periphery than does in fact exist" (Hufschmidt, 1959). The slow firing frequency of the motor units of patients with paralysis agitans is in keeping with the suggestion that muscle contraction in Parkinsonism is under the control of tension receptors rather than the length receptors of muscle. In other words, it supports the theory of interrupted gamma efferent pathways in this condition. It is not possible to say whether there is simple imbalance with "release" of tension receptor control or an actual state of overactivity of these receptors.

But the peripheral feedback is not the only source of facilitation and inhibition acting on the spinal interneurones. These are also under the controlling influence of supraspinal structures (see Chapter 1, B), and lack of facilitation or actual inhibition from these structures might result in slow firing frequency of the motor units. The findings of Bergamini et al. (1961) are specially important in this respect. They found, as stated before, that the firing frequency of the motor units increases after stereotactic operation in the thalamic region. This suggests the presence of some 'inhibitory' centre in this region of brain, 'removal' or 'damage' of which removes

its inhibitory influence on the spinal interneurones with consequent increase in the firing rate of the motor units.

So it seems that the slow firing frequency of the motor units in Parkinsonism could be due to one or more factors, such as an excess of inhibitory impulses from the tension receptors, depression of facilitatory impulses from spindles (by central gamma depression), lack of facilitation or actual inhibition from supraspinal structures - all tending to cause a rise in the threshold of the alpha motoneurones.

It is obvious that a fascinating field remains to be explored and at present no satisfactory single theory can explain all the clinical manifestations of Parkinsonism. It can only be said with reasonable certainty that the defective activity of some supraspinal structures interferes with the muscle spindle innervation in rigid muscle, the resulting block of the gamma efferents may be only 'functional' in the early stage of the disease but 'organic' changes presumably follow in a later stage (Byrnes, 1926). This would explain the loss of automatic associated movements as well as the failure to initiate voluntary movements in these patients. This difficulty is aggravated by the hypersensitivity of the Golgi tendon receptors which tends to inhibit any muscle movement reflexly. On the other hand, the retention of rapid "ballistic" movements so commonly observed (e.g. Kinesia paradoxa) may be explained on the basis of direct alpha motoneurone excitation.

CHAPTER 10

CONCLUSIONS

In the first part it was shown that the firing frequencies of motor units at particular grades of isometric contraction depend on the total number of units available for recruitment and so are regulated by length and tension receptors in the muscle. Procainisation showed the importance of the gamma-regulated length receptors in voluntary contraction. In hypertonic Parkinsonism, however, increments of voluntary contraction are presumably largely dependent on recruitment of extra units. Certainly the units recorded in the present study showed a very marked tendency to fire at unusually slow rates. They did so with a regular rhythm suggesting strong tonic inhibition. This is in contrast to the evidence reported in Chapter 8 (Paired response) pointing to the presence of motoneurone facilitation. This paradox would be solved if two antagonistic mechanisms were in action - for instance a supraspinal facilitation and a peripheral as well as supraspinal inhibitory one. Hufschmidt's (1959) work has already been discussed. He has shown that inhibitory reflexes from muscle and tendon receptors are over-active in Parkinsonism. It is now submitted that the mechanism described by him is only one of at least two important factors regulating spinal motoneurones in Parkinsonism, and it may well be that the peripheral inhibitory overaction is reactive, a regulatory reflex called into premature activity owing to the absence of the gamma regulation of the length servo (see

Chapter 9).

Further work immediately suggests itself. My colleague, R. Levy, has shown that supraspinal facilitation may be temporarily reduced by anticonvulsants and other drugs. Injection of procaine into muscle tendons will paralyse the Golgi tendon organs. Repetition of the observations reported here are planned in Parkinsonian patients after each of these procedures. It has not been a purpose of this thesis to discuss the mechanism of tremor in that disease but it may be pointed out that an interplay of two antagonistic tonic activities in spinal interneurones might lead to "oscillation of the servo-system", causing a rhythmical tremor which would not require presence of the same rhythmicity in a descending extra-pyrimidal outflow.

For normal physiology this work emphasizes the importance of peripheral regulatory systems in the performance of voluntary movement, and is in complete accord with the suggestions of Granit and his school. The unexpected findings in Parkinsonism and in Friedreich's ataxia suggest a further parameter of control which could not be detected by workers with animals in which the activity investigated can scarcely be termed "voluntary". It has been accepted since the work of Adrian and Bronk (1929) that the tension of voluntary contracted muscle is raised by increasing the firing rates of motor units to a certain limiting value (possibly related to tetanus fusion frequency: see Chapter 3) and also by recruitment of new units. The present study shows that these controls are affected differentially by disease. Simpson (personal communication) suggests that supraspinal

facilitation may control the recruitment of alpha motoneurones while the gamma loop regulates their firing frequency. This hypothesis should be tested by animal experiment.

APPENDIX

PREPARATION OF THE MICROELECTRODE

A steel sewing needle was erroded electrochemically (Bishop and Collin, 1951) till the tip was reduced approximately to 20 μ in diameter. It was then varnished* and baked at 200°C for 6 minutes after each layer of varnish was applied. The process was continued till the whole of the shaft of the needle was covered with varnish except the very tip. Ten to fourteen layers of varnish were applied to accomplish the required end-result. A flexible lead was soldered to the other end of the needle. Needles were examined with a microscope and only those of the required tip dimension and insulation were selected for use. Needles of this type were used by Purpura and Chatfield (1952) and Norris and Gasteiger (1955), who found that, with suitable siting of the tip, it was possible to observe the activity of a single motor unit of a muscle throughout most of a voluntary contraction.

* The type of varnish used was V.7132, Hymeg No. 4, supplied by Lewis Berger (Scotland Ltd.) of Forbes Street, Glasgow.

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ACKNOWLEDGMENT

I wish to record my sincere gratitude to Dr J.A. Simpson for suggesting the problem and for his great interest, helpful guidance and encouragement in the course of the present work and in the preparation of this thesis.

I am thankful to him as well as to Dr J.B. Stanton for kindly allowing me to experiment on different patients admitted under their care in the Northern General Hospital (Neurological Unit).

Thanks are also expressed to Professor K.W. Donald for his interest and encouragement, and to my friend and colleague Mr J.M.M. Neilson for his invaluable suggestions and unfailing help at different difficult stages of the present work.

This work was carried out during the tenure of a University of Edinburgh, Faculty of Medicine Graduate Research Fellowship (from February, 1960 to January, 1962).